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STUDIES IN LIPID PNEUMONIA

I. LIPID PNEUMONIA DUE TO COD LIVER OIL

II. LIPID PNEUMONIA DUE TO LIQUID PETROLATUM

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During the past five years 22 cases of lipid [1] pneumonia have been studied at Bellevue Hospital. Differential histochemical studies of the lipid were made in each case; in 7 instances these studies were supplemented by chemical analysis, which corroborated the conclusions drawn from histologic observations. A review of the literature shows that except for Pinkerton's [2] report and a few isolated case reports little attention has been paid to the various tissue reactions induced by different lipids, and no comprehensive studies of lesions in man showing these differences beyond reasonable doubt have been recorded.

Laughlen's [3] report in 1925 was the first to reveal some of the distinctive pulmonary alterations in man attributable to an oily substance. He found (in 4 infants and 1 adult) consolidation characterized by an alveolar exudate of vacuolated macrophages which dissolved sudan III. According to the clinical records, liquid petrolatum had been used as "nose drops" or as a laxative, and, without further identification, he inferred that it had been aspirated in these patients. He reproduced

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1. A variety of terms has been applied to the condition of lungs showing inflammation associated with the deposit of exogenous lipids. The most widely used term "lipoid pneumonia" is incorrect, since the use of the adjective "lipoid" alleges a resemblance to oil or fat; further, the whole phrase is ambiguous in that it does not indicate whether the pneumonic zone resembles a lipid or is associated with a lipid. The many other terms include "lipoid cell pneumonia," "oil aspiration pneumonia," "pneumonoliposis," "elainosis," "paraffinosis," "pulmonary oil tumors" and "oil pneumonia." The term "lipoid cell pneumonia" is inadequate because some lipids elicit a purulent reaction with few macrophages and give rise to other histologic changes in later stages. Some of the other terms are awkward or limited in meaning. The term "lipid pneumonia" seems etymologically correct and indicates that the inflammation is due to any oil or related lipid.

2. Pinkerton, H.: Am. J. Dis. Child. **33**:259, 1927.

3. Laughlen, G. F.: Am. J. Path. **1**:407, 1925.

the exudate in the lungs of rabbits by intratracheal or pharyngeal instillation of liquid petrolatum.

In clinical and experimental reports of the pulmonary changes due to fats and oils, Pinkerton [4] showed that there are several phases of the subject. He described the changes which he observed in the lungs of 6 infants and decided that the pulmonary reaction was primarily an outpouring of macrophages with subsequent formation of giant cells and fibrosis. By studying the staining reactions, solubility and other characteristics of the material in the lungs of these infants, he was able to show that several different kinds of oil [5] were present. In the experimental study he demonstrated many differences in reactions to oils of vegetable, mineral and animal origin. From observations on puppies and rabbits he concluded that lipids and oils injected intratracheally disappear slowly from the lungs and that the simple neutral vegetable oils provoke practically no reaction. In contrast, animal oils cause marked fibrosis and formation of giant cells in a few days. He observed that liquid petrolatum becomes quickly emulsified in fine droplets and is engulfed by phagocytic cells and that it produces patchy and confluent consolidation.

Pinkerton's observations on the pulmonary reaction to cod liver oil warrant special mention. He asserted that this oil produces slow necrosis of the tissue and exhibits changes in staining reactions, and he concluded that it undergoes hydrolysis. He found that after various periods in the lung cod liver oil becomes insoluble in ordinary fat solvents and acquires an affinity for carbolfuchsin and that it resists decolorization by acid alcohol as much as does the tubercle bacillus. He attributed this acid-fastness to oxidation or "blowing"—similar to the change seen in drying oils. By passing air through cod liver oil, he said, a thick gummy substance was obtained which was nearly insoluble in ether and chloroform and which when stained with carbolfuchsin was resistant to decolorization. My associates and I have observed acid-fast material in the lungs of infants who had aspirated

4. Pinkerton, H.: Arch. Path. **5**:380, 1928.

5. The irritating power of other lipids in causing human pulmonary disease has been explored very little. "Arachidic bronchitis" is the term introduced by Jackson and Spencer (J. A. M. A. **73**:672, 1919) to denote the pulmonary lesion which may follow aspiration of a peanut. Clausen and Heatly (Arch. Otolaryng. **11**:569, 1930) have shown that this lesion is attributable to the irritating power of the lipid in peanuts and specifically to the highly irritating activity of the unsaturated oleic acid. The acute inflammation induced by this lipid is like that seen with cod liver oil. There is reason to believe that other vegetable oils possessing unsaturated fatty acids are equally irritating. Croton oil has been used to induce inflammation in commonplace laboratory experiments. In unpublished experiments with castor oil and peanut oil my associates and I have found that the earliest response to these is an acute seropurulent inflammation. It seems wiser, therefore, to study the reaction to each lipid before labeling one group as less irritating than another.

cod liver oil, but some of our observations and our interpretation are at variance with those of Pinkerton and will be discussed in detail later in this article.

Of particular interest is the first complete report on an adult with "lipid pneumonia," contributed by Fischer-Wasels [6] in 1933. Under the title "Fatal Pulmonary Cirrhosis from the Use of Menthol Oil," he recorded the first chemical analysis of a lipid extracted from a pulmonary lesion. His patient, a woman of 70, exhibited cirrhotic lesions in the lower lobes of both lungs. At necropsy both lungs showed masses in the hilar regions with replacement of the lung tissue by scar tissue. In the clefts between the bands of connective tissue there were large homogeneous masses which stained light red with scarlet red. With this finding, reinvestigation of the patient's clinical record revealed that she had been receiving menthol in oil in large quantities by nasal instillation for twenty years. Fischer-Wasels estimated (from the analysis) that there was about 100 cc. of liquid petrolatum in her lung. After determining that the extracted oil was unsaponifiable and was not cholesterol, he inferred that it was liquid petrolatum.

Following these studies, there has been a steady increase of reports of this disease under various titles. The largest experience has been reported by Goodwin [7] among infants and children at the Harriet Lane Home of the Johns Hopkins Hospital. Twenty-five cases of "lipoid cell pneumonia" were observed there in a ten year period. In summarizing the brief observations on the pathologic picture found at necropsy he noted marked variations attributable to the age of the process, the presence and amount of secondary infection and the type of oil aspirated. These observations confirmed the descriptions of Laughlen and Pinkerton.

This and other reports bring out the frequency of this type of aspiration pneumonia in infants, especially in those prematurely born, congenitally defective, debilitated or suffering from neurologic disorders in which deglutition may be impaired. The occasional cases in which the condition develops in a previously healthy baby after forced feeding or following the use of "nose drops" are particularly important because they emphasize the role of aspiration of nasopharyngeal contents.

Recently, lipid pneumonia in adults has been receiving attention. Ikeda [8] collected 5 cases in his own laboratory and analyzed 38 cases

6. Fischer-Wasels, B.: Frankfurt. Ztschr. f. Path. **44**:412, 1933.
7. Goodwin, T. C.: Am. J. Dis. Child. **48**:309, 1934.
8. Ikeda, K.: Arch. Path. **23**:470, 1937.

found recorded in the literature.[9] He suggested that among adults a more chronic and tumor-like process is the typical finding when the pneumonitis is due to liquid petrolatum; he expressed the belief that it develops over a period of years, accompanied by recurrent broncho-pulmonary symptoms. He stressed the clinical and roentgenographic resemblances to pulmonary neoplasm, stating that there was even a macroscopic resemblance at necropsy, and concluded that the lesion is essentially a "paraffinoma" of the lung. Cases in which chronic pneumonitis with a tumor-like lesion of the lung proved to be due to liquid petrolatum have been recorded by Houck[10] and Klinck.[11]

Since 1935, when I[12] reported various types of lipid pneumonia as observed in 6 infants and adults, I have encountered this condition in 16 additional patients at Bellevue Hospital. To emphasize the differences in the reactions the chief findings in all cases have been tabulated. The consistent observation of acid-fast membranes around aspirated cod liver oil, together with other points of difference, warranted separating the lesions due to this lipid from those induced by liquid petrolatum. Altogether, there were 13 infants and 9 adults—all but 1 of the infants were encountered at necropsies between 1934 and 1938; the adults were met with during the same period. The data were correlated with clinical information bearing on the use of oily substances in the diet or in the treatment of each patient when such information was available.

MATERIAL AND METHODS OF STUDY

Fixation and Staining.—In every case, following postmortem examination, the tissue had been preserved in dilute solution of formaldehyde U. S. P. (1:10) for varying periods. In some instances, when reexamination of old sections suggested the presence of oil, tissue stored two to eight years was found to contain oil. In every instance frozen sections were stained with osmic acid, sudan IV and nile blue sulfate. Unstained sections were examined polariscopically for cholesterol esters, and paraffin sections of formaldehyde-fixed and osmic acid–fixed tissue were studied with differential stains. These included stains for reticulum, fibrin and bacteria and the Ziehl-Neelsen stain for acid-fast substances. Original paraffin blocks were used for the application of special stains when acid-fast material was

9. Of the 43 patients, 22 came to necropsy. The rest were considered to have lipid pneumonia because of distinctive persistent and progressive opacities in the lower pulmonary fields in roentgenograms. These findings together with a history of nasal or laryngeal instillation of liquid petrolatum were considered sufficient to support the diagnosis. Of the cases in which postmortem observations were available, many are of limited value because the attempts to identify the lipid found were insufficient.

10. Houck, G. H., in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 463.

11. Klinck, G. H., Jr.: Albany M. Ann. **55**:71, 1936.

12. Graef, I.: Am. J. Path. **11**:862, 1935.

being sought. It was found, however, that in some instances the acid-fast material found in original paraffin blocks could still be detected in formaldehyde-fixed material after eight years.

Chemical Analysis.—Formaldehyde-fixed tissue was weighed wet, cut in small strips and ground with a known amount of glass powder. The ground material was placed in a weighed thimble and placed in a Soxhlet apparatus. The material was covered with 95 per cent alcohol and allowed to stand overnight. It was then extracted for about four hours with alcohol and the extract filtered into a volumetric flask. Extraction of the material was resumed with ether. The ether extract was filtered and added to the alcohol extract and the contents of the volumetric flask made up to volume. The thimble (containing glass powder and dry residue) was dried and weighed; deduction of the weight of the thimble and glass powder yielded the dry weight of the fat-free sample.

From the known volume of the extract an aliquot was taken and evaporated; to the dry but still warm residue was added petroleum ether and the whole allowed to stand overnight. Then the petroleum ether was filtered into a weighed flask, evaporated and placed in a desiccator overnight. The weight of the residue yielded total lipid.

The lipid thus obtained was saponified with five times normal sodium hydroxide in 95 per cent alcohol under a reflux condenser for about two hours, cooled, transferred to a separatory funnel and shaken out several times with petroleum ether. The combined petroleum extracts were washed several times with 50 per cent alcohol, placed in a weighed flask and evaporated. The flask was placed in a desiccator overnight, and the residue, which was considered to be the unsaponifiable material, was weighed.

The alkaline solution was acidified and extracted with petroleum ether several times in a separatory funnel. The petroleum ether extracts were mixed and the ether evaporated. The residue was placed in a desiccator and weighed. This value was considered to be that of the true fatty acids.

The cholesterol content of the unsaponifiable material was determined by the colorimetric method of Bloor.

The iodine number of several of the lipids recovered was determined by the method of Yasuda.

I. LIPID PNEUMONIA DUE TO COD LIVER OIL

Tables 1 and 2 summarize the pertinent data on 7 infants who came to necropsy with pulmonary lesions attributable to cod liver oil. The cases naturally fall into two groups. In 4 (cases 1, 2, 3 and 4) there were relatively fresh lesions with signs of widespread or massive aspiration of oil—the oil even obstructing the bronchioles. The second group consists of 3 cases (5, 6 and 7) in which the changes were more advanced, suggesting that the lesions were older and were produced by the oil some time before death.

GROUP 1. EARLIER LESIONS

In the 4 cases in which the lesions were fresh there was widespread acute fibrinopurulent inflammation of the bronchioles and pulmonary lobules, much extracellular oil and widespread alveolar necrosis (beginning abscess formation in 1 case). The most distinctive feature

TABLE 1.—*Lipid Pneumonia in Infants Due to Aspiration of Cod Liver Oil: The Early Reaction*

	Case 1	Case 2	Case 3	Case 4
Age	2½ months	4 months	4½ months	16 months
Clinical diagnosis	Bronchopneumonia; congenital heart disease	Mongolism; gonorrheal conjunctivitis mastoiditis; "lobar" pneumonia	Bronchopneumonia; acute otitis media; sepsis	Broncholobular pneumonia; multiple skeletal anomalies
Hospital stay	2½ months	2 months	4½ weeks	15½ months
Fever	None	Low fever, 104 F., last 3 days	Irregular, high	High fever last 10 days
Pulmonary signs	Cyanosis and dyspnea last 3 days	None	Cough; rales at right base from admission	Signs of consolidation in right lung (see text)
Roentgen examination	None	Irregular shadows in both upper lobes 2 days ante mortem	"Increased interstitial markings in upper lobes"	Consolidation in right lung and left lower lobe
Other clinical observations	Repeated vomiting for 5 days ante mortem; gavage 3 days ante mortem	Occasional projectile vomiting; unexpected death	Gavage followed by choking on day of death	(See text)
Lipid, dose and administration	Cod liver oil, 4 cc., 3 times daily for 3 weeks ante mortem; albolene "nosedrops" 3 days ante mortem	Cod liver oil, 4 cc., 3 times daily for 1 month ante mortem; ephedrine in oil intranasally, 2-4 cc. daily first 3 weeks in hospital	Viosterol, 3 cc., daily for 16 days; mineral oil to lips occasionally; no record of cod liver oil	Cod liver oil, 2-4 cc., daily for 15½ months; mineral oil, 10 drops by mouth occasionally; viosterol occasionally
Pathologic pulmonary changes	Patchy yellowish red consolidation in right upper and right middle lobes; cloudy semiliquid yellowish material in bronchi	Patchy lobular consolidation, red on section	Confluent broncholobular pneumonia	Confluent lobular (lobar) pneumonia all lobes, butter yellow or grayish yellow on section
Microscopic changes	1. Asphyxial type of bronchial obstruction by bile salts, globules of emulsified oil and coagulated protein debris 2. Focal alveolar exudate of polymorphonuclear leukocytes 3. Extensive extracellular formation of acid-fast membranes around free oil	1. Discrete and confluent sanguinopurulent lobular pneumonia 2. Reaction concentrated around globules of extracellular oil 3. Focal necrosis of alveolar walls near oily masses 4. Extracellular acid-fast membranes around oil and traces within macrophages	1. Bilateral confluent broncholobular pneumonia with marked necrosis 2. Many masses of extracellular oil surrounded by acid-fast membranes	1. Confluent fibrinopurulent pneumonia with marked necrosis of exudate 2. Widespread acid-fast membrane formation around masses of extracellular oil
Histochemical examination				
Sudan IV	Orange	Orange	Orange	Orange
Nile blue sulfate	Dark blue	Dark blue	Dark blue	Dark blue
Osmic acid	+	+	+	+
Ziehl-Neelsen*	+ membranes	+ membranes	+ membranes	+ membranes
Polariscopic	0	0	0	0
Other pathologic conditions	Patent foramen ovale	Albinism; interauricular and interventricular septal defects		

* This stain was used to determine the presence of acid-fast material.

was the acid-fast hyaline membranes around the oil. Case 4 illustrates this group and is therefore given in detail.

Case 4.—A 16 month old girl had been in Bellevue Hospital all her life. She was born at term and had congenital skeletal deformities of both arms and legs. At 15 months she weighed 8 pounds 11 ounces (8,476.5 Gm.). Nine days before death there were high fever, vomiting, leukocytosis, signs of consolidation at the apex of the right lung and rales at the bases of both lungs. The clinical diagnosis was "broncholobular" pneumonia. Pneumococcus type VI was recovered from the throat. She died after a stormy course.

Significant Observations at Autopsy.—The body was that of a poorly nourished infant with the congenital anomalies noted in life. The pleural sacs were free of

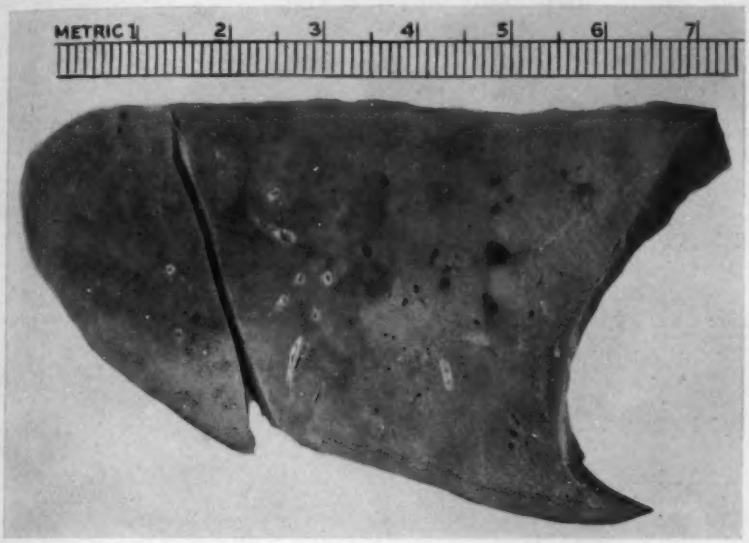

Fig. 1 (case 4).—Cut surface of a section through the upper and lower lobes of the right lung, showing the consolidated appearance. The darker zones were yellow-brown, and the rest of the surface was yellow.

fluid and adhesions. The right lung was solid. Section revealed a striking golden yellow surface with a few pinkish zones.

The upper and lower lobes of the right lung (fig. 1) were consolidated, and the lobular markings were readily made out. In the middle lobe of the right lung the lobular consolidation was limited to the area near the hilus. The upper lobe of the left lung presented the same appearance. In the lower lobe of the left lung the consolidated lobules were noted in the upper third close to the interlobar fissure. The trachea and bronchi were inflamed and showed engorgement of the mucosa and a frothy mucopurulent exudate.

The paratracheal lymph nodes were markedly enlarged and seen as discrete, juicy, reddish gray masses, pink on section. The other organs showed no notable changes.

Microscopic Observations.—Most lobules of all three lobes of the right lung (figs. 2 and 3) contained an inflammatory exudate, more or less filling the lobules, made up of polymorphonuclear leukocytes, mononuclear cells and a few red cells. The alveolar septums of other lobules appeared necrotic (fig. 4), and the sacs were filled with serum, fibrin and a few cells. In the lumens of many alveoli, usually adjacent to the alveolar walls, a deeply eosinophilic membrane was found; in some

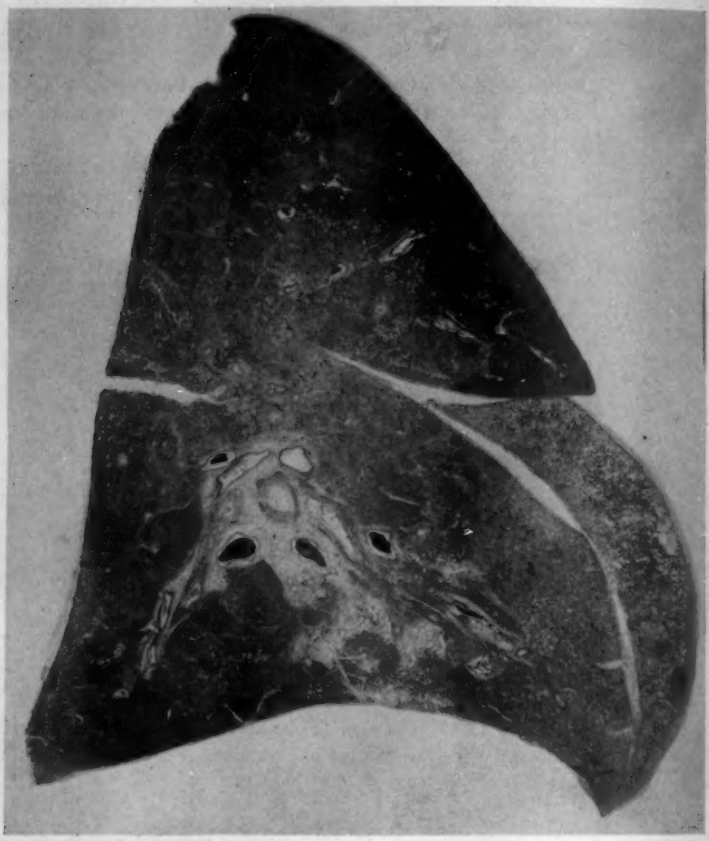

Fig. 2 (case 4).—Whole lung section of the right lung, showing the fairly intact middle lobe and the confluent consolidation of the upper and lower lobes.

areas it was vacuolated. In some alveoli it appeared as a circular membrane, 15 to 25 microns in thickness, surrounding a mass of oil; elsewhere it was found as a semicircular band or as a fragment. With osmic acid (fig. 5) it was yellowish gray and was found to surround free masses of blackened oil. Counterstained with carbolfuchsin and decolorized with acid alcohol, the same membranes appeared as fairly sharp, highly refractile, purplish pink bands (fig. 6). Sudan IV and nile

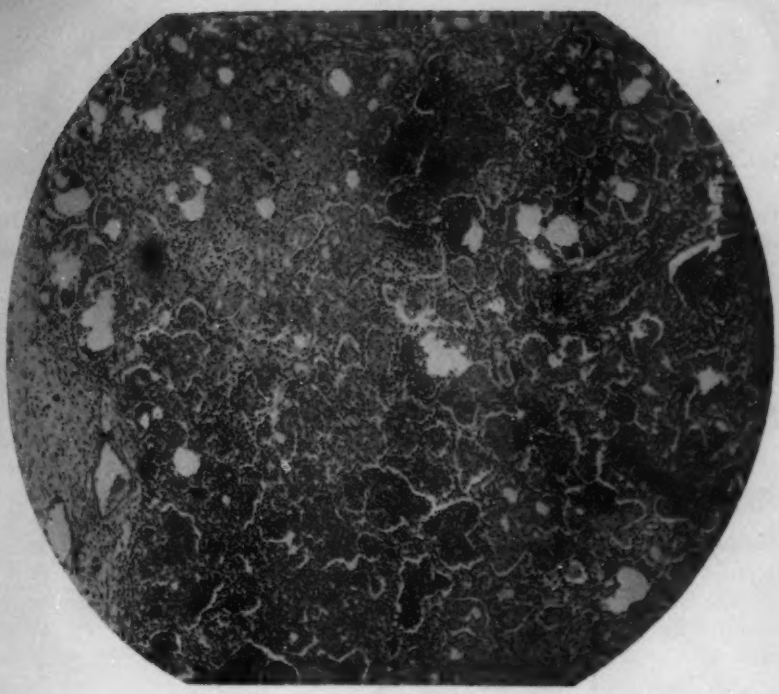

Fig. 3 (case 4).—Low power photomicrograph of a paraffin section, showing the mixed appearance of the exudate; in some places it is fibrinous and the alveolar cells have sloughed off; elsewhere it is fibrinopurulent. Lipid stain demonstrated free lipid in the spaces (see fig. 5).

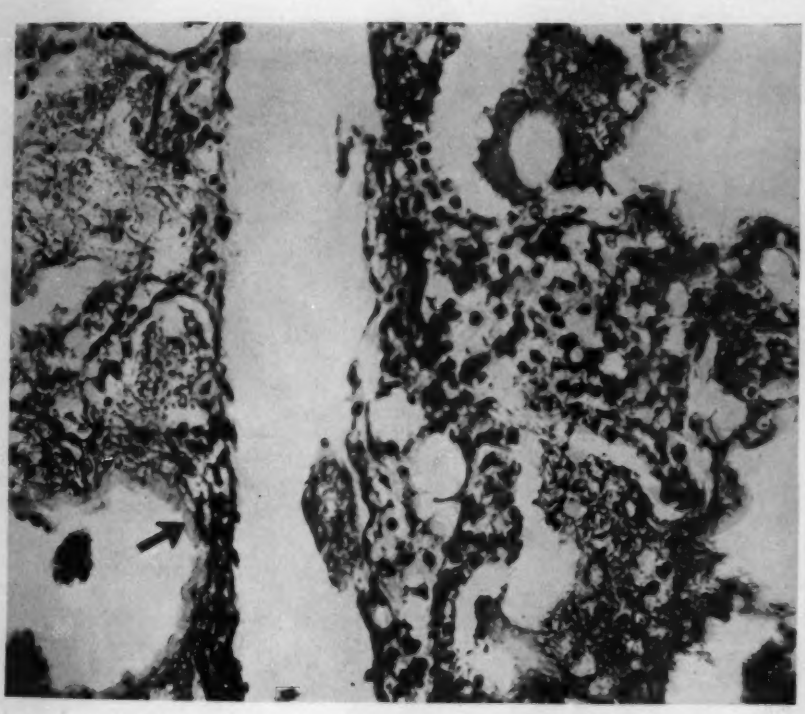

Fig. 4.—High power photomicrograph of the section shown in figure 3. The arrow points to the hyaline refractile membrane clinging to the alveolar wall. This is acid fast and surrounds a mass of oil dissolved out by the paraffin solvents. The adjacent alveoli contain globules of oil, fibrinous threads and leukocytes.

blue sulfate [13] stained the free oil and the membranes [14] in the same manner, and blocks from different portions of both lungs revealed huge quantities of free oil. In frozen sections the membranes could not be seen separated from the oil as they could in paraffin sections.

A few doubly refractile granules and globules were demonstrable on polariscopic examination of frozen sections.

There was focal infiltration of the septums by mononuclear cells, and many contained fatty droplets which stained like the free lipid.

The lumens of many bronchioles contained numerous polymorphonuclear leukocytes. There was a small amount of free oil in the lumens of a few, and some exhibited moderate mononuclear infiltration of their walls. In the interlobular septums there was focal infiltration by polymorphonuclears, and an early inflammatory exudate was found in the visceral pleura. Patchy emphysema was present in a few less affected lobules.

The left lung presented a similar picture. The upper lobe was almost entirely involved in the inflammatory process, while the lower half of the lower lobe was spared.

The bronchial lymph nodes stained for fat showed traces of lipid material in a few macrophages. The rest of the organs showed no significant changes.

Final Diagnosis.—The diagnosis was confluent lobular pneumonia, focal lobular necrosis, widespread aspiration of lipid, acute suppurative endobronchitis and focal acute pleuritis.

The findings in this case could not be attributed to cod liver oil only, for a pure growth of Pneumococcus type VI was obtained on postmortem culture of the lungs, and the same type was recovered from the throat ante mortem. However, experience with other cases and experimental studies of the histologic reaction to cod liver oil have shown that cod liver oil alone can produce the picture found here (fig. 7), even to the widespread confluent acute fibrinopurulent exudation. Marked pleuritis and inflammation of the interlobular septums, so regularly found in pneumococcic infections of the lung, were lacking, which further incriminated cod liver oil as the chief irritant.

The first macroscopic examination of the lung did not arouse a suspicion of the presence of aspirated lipid, and the first microscopic

13. Pinkerton in an early study of staining reactions of various lipids described the reaction with nile blue sulfate as resulting in a salmon color. My associates and I have been unable to confirm this. Both in human lesions and in experimental lesions produced with cod liver oil and halibut liver oil we have found the staining reaction to be dark blue or bluish purple.

14. Sudan IV stains were applied to paraffin sections in these cases after we learned how insoluble the acid-fast membranes are. This stain further demonstrated the presence of an insoluble lipid. It is simple to use on paraffin sections, which are mounted in glycerin after staining, and thus the alcoholic reagents, which would dissolve the dye, are avoided.

studies gave few clues to the presence of oil. There were few macrophages, and the exudate was chiefly fibrinopurulent. Because the zones of necrosis suggested the possibility of a tuberculous inflammation, Ziehl-Neelsen staining was carried out and revealed the acid-fast membranes. Lipid stains were then used on frozen sections, and a

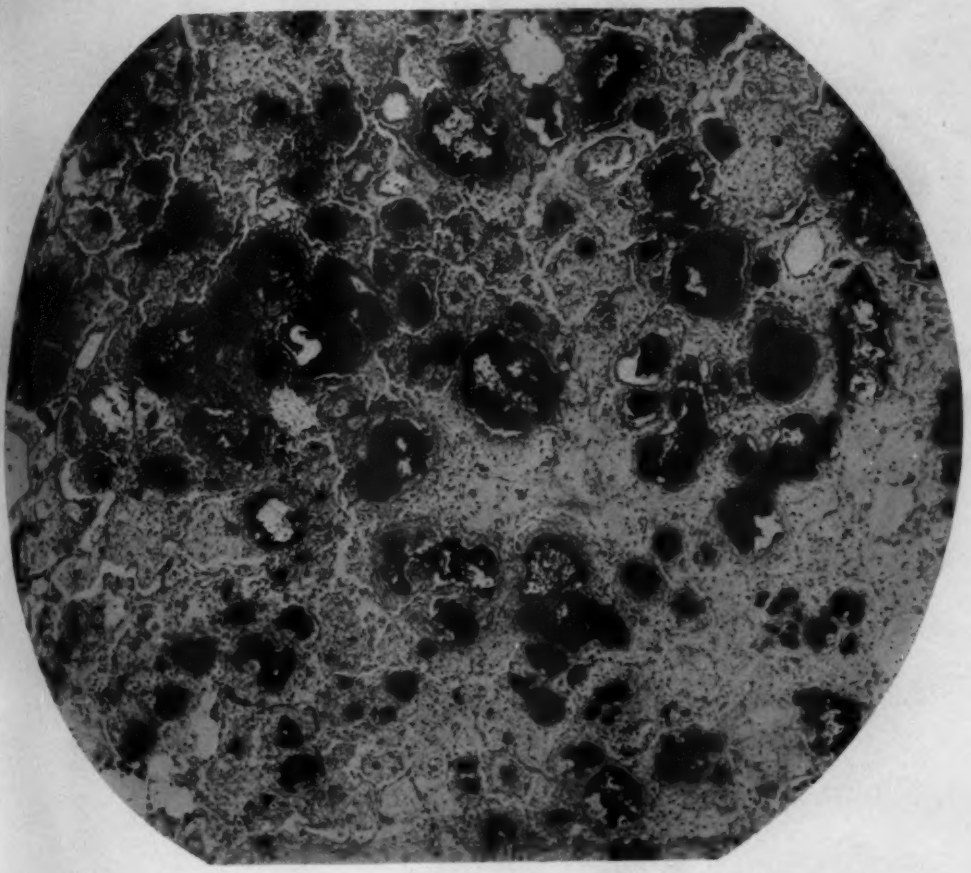

Fig. 5 (case 4).—A section from a block of tissue from the right lung which was immersed in osmic acid after fixation. Note the irregular outline of the oily masses. Close inspection shows the hyaline membrane at their surfaces as a dark grayish band.

piece of fixed tissue was washed and treated with osmic acid, with the results described. The nature of the acid-fast material is discussed in detail later.

In the other 3 cases (1, 2 and 3) similar lesions were shown on a smaller scale. In all cases extracellular acid-fast membranes were

exhibited around free oily globules and masses. Case 1 was distinguished for massive obstruction of the bronchioles (fig. 8) by partly emulsified oil globules. In all 4 instances the oil was rarely encountered in spherical globules. It usually appeared in uneven

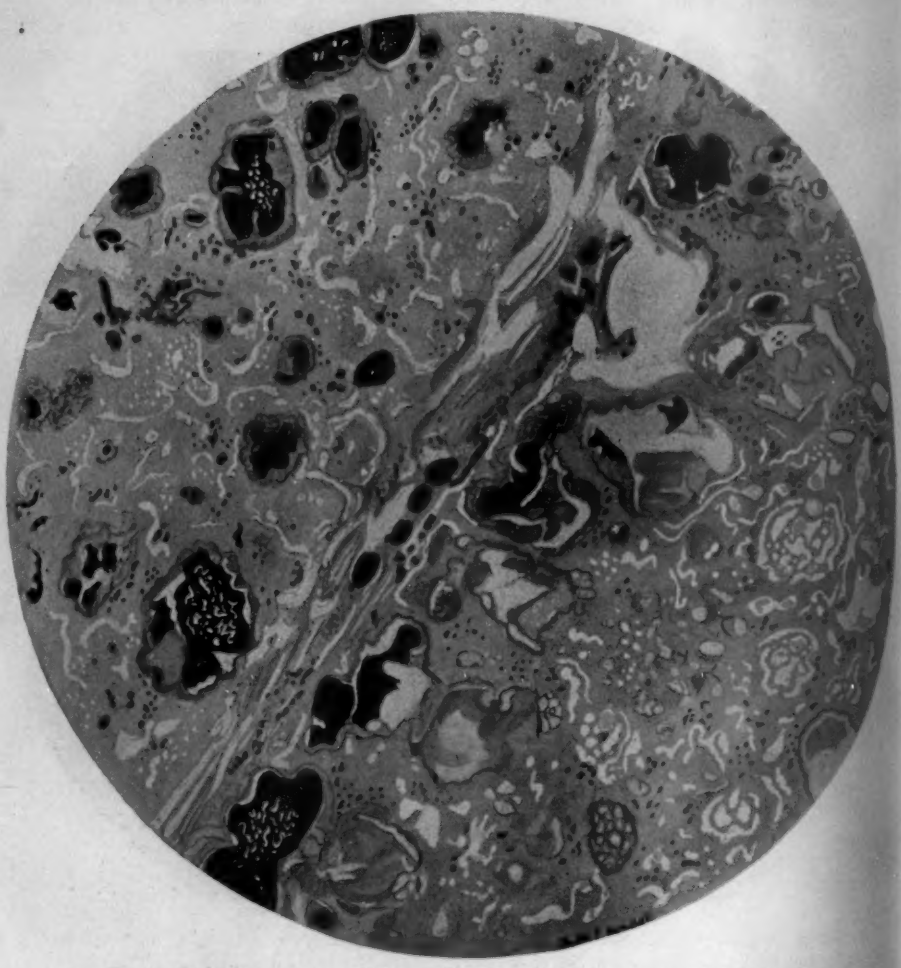

Fig. 6.—Drawing of a field in a section of the same osmic acid–immersed block shown in figure 5. The section was counterstained by the Ziehl-Neelsen method. The hyaline membranes are all acid fast and invest the irregular masses of oil which have not been dissolved out in handling.

lobulated or shreddy masses, invested by the membranes. This suggested that when the membranes had formed, they contracted and deformed the surface of the oily masses.

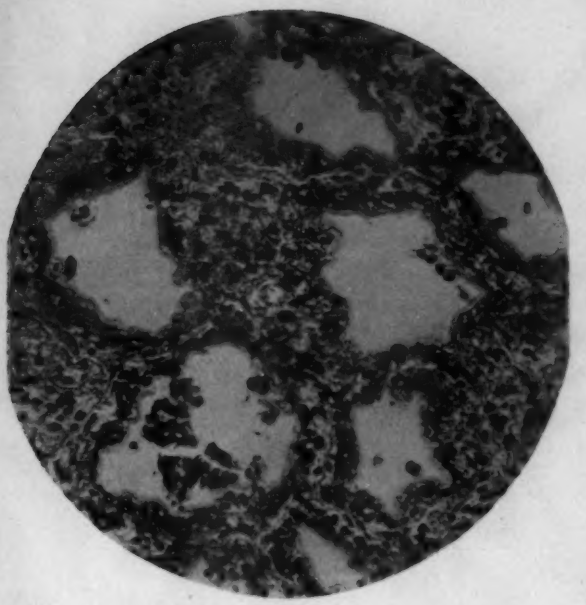

Fig. 7.—Photomicrograph of a paraffin section of the lung of a monkey forty-eight hours after an injection of cod liver oil. A diffuse fibrinopurulent exudate is present, and the alveoli are lined by a hyaline acid-fast membrane like that shown in figure 4. The clear spaces in the alveoli contained soluble oil, which was dissolved out by the paraffin solvents.

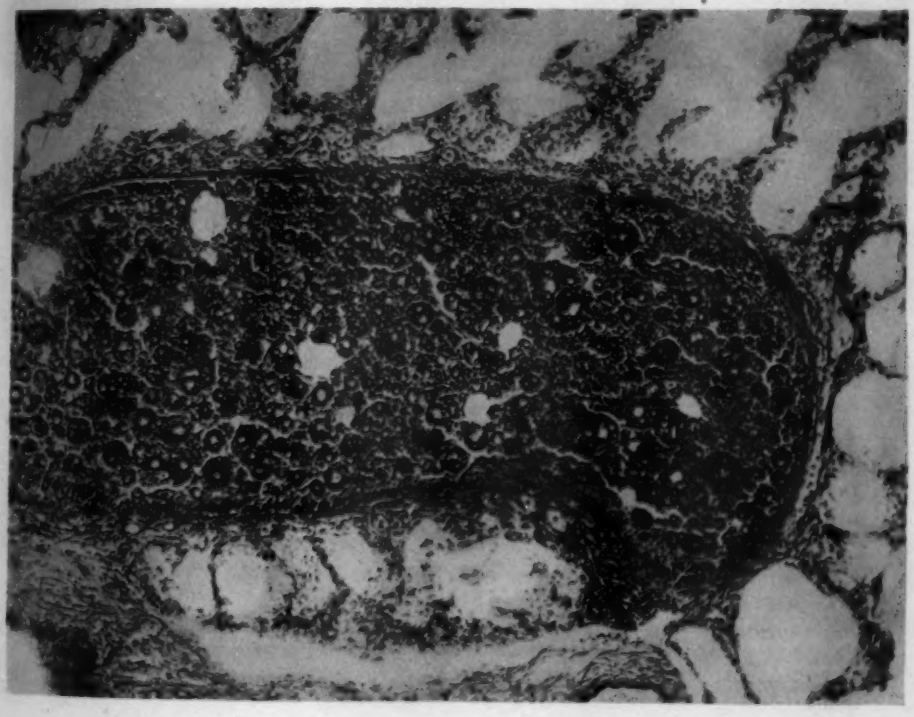

Fig. 8.—Photomicrograph of a cross section of a bronchiole filled with emulsified oil droplets and masses, around which fine acid-fast membranes formed (case 1).

Chemical extraction for lipid was done in case 4 (see table 2) and showed that the samples examined contained between five and six times as much lipid as normal. The high content of saponifiable material and the iodine value of the lipid, together with the low content of unsaponifiable lipid, support the histochemical results and at least exclude liquid petrolatum.

TABLE 2.—*Results of Analyses for Lipid in Two Cases of Pneumonia Associated with Aspiration of Cod Liver Oil*

Case	Lipid Implicated	Sample: Dry Weight, Gm.	Sample: Wet Weight, Gm.	Total Lipid, Gm.*	Percentage of Dry Weight	Total Saponifiable Lipid, Gm.	Percentage of Total Lipid	Total Unsaponifiable Lipid, Gm.	Percentage of Total Lipid	Iodine Value on Total Lipid	Cholesterol, Gm.	Percentage of Cholesterol in Unsaponifiable Lipid	Percentage of Cholesterol in Total Lipid
4	Cod liver oil	8.3	1.34	0.755	58	0.465	61.6	0.148	19.6	47.7	+	?	..
7	Cod liver oil	6.7	0.927	0.172	18	0.107	62	0.025	14	45.7	0.019	73.5	11
		17	1.95	0.278	14	0.133	47	0.077	27	....	0.043	57	15
		5.14	0.517	0.08	15	0.047	58	0.012	15	48.3			

* From 2 to 3 per cent of wet normal lung when washed free from blood and mucus may be lipid; this is 10 to 16 per cent when calculated from dry weight (Pincussen, in Oppenheimer, C.: Handbuch der Biochemie des Menschen und der Tiere, Jena, Gustav Fischer, 1909-1913, vol. 4, p. 289).

Note the large quantity of total lipid in case 4, in which there was massive aspiration of cod liver oil and the bulk of this lipid was saponifiable. In case 7 only traces of cod liver oil were demonstrated histologically, and the total lipid was not significantly increased over normal.

GROUP 2. OLDER LESIONS

In the second group (table 3) the reaction to aspirated oil appears older, for in these cases much of the lipid and many of the acid-fast membranes are intracellular. In cases 5 and 7 both intracellular and extracellular oil and membranes were found, and this response may be intermediate in duration. Case 7 illustrates the older group best and is therefore given in detail.

CASE 7.—A 5 month old white boy was readmitted to Bellevue Hospital Jan. 14 and died Jan. 22, 1936. He weighed 8 pounds (3,628.7 Gm.) at birth. He was first admitted to Bellevue Hospital at the age of 23 days for nasopharyngitis of five days' duration. He was discharged after seventeen days and readmitted three days later, Oct. 3, 1935, because of cough and continued nasal discharge. Except for a few rales heard throughout the left lung anteriorly and posteriorly and in the right interscapular region, there were no new findings. The clinical diagnosis was bronchitis. As before, he was given "ephedrine nose drops."

With improvement, he was sent home only to be readmitted October 21 because of onset of diarrhea the day before. There was a slight cough. Physical examination revealed moderate undernourishment and an occasional resonant rale over the pulmonary fields. Viosterol, 0.15 cc., was given twice daily and then replaced by cod liver oil, 2 cc., twice daily, beginning October 24. November 4, after some

improvement, he was sent to a convalescent nursery, where he received a mixed formula and cod liver oil, 4 cc., twice daily. Jan. 14, 1936, he became suddenly ill, seemed to be "all choked up" and was said to have a cold. He was readmitted

TABLE 3.—*Lipid Pneumonia of Infants Due to Aspiration of Cod Liver Oil: The Late Reaction*

	Case 5	Case 6	Case 7
Age	11 months	4 months	5½ months
Clinical diagnosis	Bronchopneumonia; otitis media; sepsis	Congenital syphilis; marasmus	"Lobar" pneumonia
Hospital stay	13 days	4 weeks	7 days
Fever	High, continuous	None	High, continuous
Pulmonary signs	Cyanosis	None recorded	Signs of consolidation in right upper and middle lobes; cyanosis +
Roentgen examination	Film and report lost	Not done	Consolidation in right upper and middle lobes
Other clinical observations	Vomiting after meals 4 days; lavage done twice	Recurrent vomiting	Choking and cyanosis on day of admission, unexplained (see text)
Lipid, dose and administration	Cod liver oil, 4 cc., 3 times daily; albolene "nose drops" daily, dose ?	Cod liver oil, 4-8 cc., daily for 19 days; viosterol, 10 drops daily for 13 days	Cod liver oil, 4 cc., daily for 3 months; viosterol, 3 drops daily for 3 days ante mortem
Pathologic pulmonary changes	Patchy lobular consolidation, left lower lobe; greenish foreign material (gastric contents) in bronchi	Patchy lobular consolidation, right lower lobe, yellowish gray on section	Lobar consolidation, right upper and middle lobes; acute fibrinous pleuritis
Microscopic changes	1. Focal fibrinopurulent pneumonia and endobronchiolitis with focal necrosis and fresh abscess formation 2. Extracellular acid-fast membranes around free oil and intracellular acid-fast granules, rings and filaments within macrophages	1. Focal necrosis in zones of consolidation with beginning cavity formation 2. Foreign body giant cells and foamy macrophages in same zones with extracellular and intracellular acid-fast membranes around oil	1. Confluent fibrinopurulent pneumonia, right upper and middle lobes 2. Focal interlobular histiocytic proliferation 3. Focal exudate of epithelioid monocytes and foreign body giant cells in some lobules and occasional foamy macrophages containing acid-fast rings and droplets around lipid 4. Some free lipid with acid-fast membrane
Histochemical examination			
Sudan IV	Red	Orange-red	Orange-red
Nile blue sulfate	Dark blue	Dark blue	Dark blue
Osmic acid	+	+	+
Ziehl-Neelsen*	+ membranes, granules, occasional droplets, rings (intracellular and extracellular)	+ membranes, rings, droplets (intracellular and extracellular)	+ granules, droplets, rings and filaments (intracellular)
Polariscopic	0	++ scattered droplets	0
Other pathologic conditions	Acute mastoiditis	Syphilitic osteochondritis; interstitial fibrosis of spleen and kidney	Pneumococcus XIV in sputum (?)

* This stain was used to determine the presence of acid-fact material.

to the Children's Medical Service, and physical examination revealed an acutely ill infant with a slight purulent nasal discharge, congestion of the pharynx, and fine and medium moist rales over the right upper pulmonary field. Respirations were rapid, and there was considerable coughing. Fluoroscopic examination showed an

indefinite shadow in the middle of the right pulmonary field. The pulmonary signs persisted over the right side of the chest and were accompanied by an expiratory grunt.

The temperature ranged from 102 to 105 F.; the leukocyte count was 14,400, with 72 per cent polymorphonuclears. The urine was normal except for a trace of acetone. A throat swab yielded pneumococcus type XIV.

Slight cyanosis supervened; a new roentgenogram revealed involvement of the right middle lobe as well. Respirations became very rapid, 60 to 70 per minute; the cyanosis increased, and the child died on January 22. The clinical diagnosis was lobar pneumonia, involving the right upper and middle lobes, with pleuritis.

Significant Observations at Autopsy.—The body was that of a fairly well nourished white boy of 5 months, weighing 12 pounds (5,443 Gm.). There were no external abnormalities worthy of note; there was no clubbing.

When the thorax was opened, the lungs were seen to overlap the precordial area. The left pleural sac was normal and contained no fluid. On the right side the lung was bound to the parietal pleura by thin fibrinous adhesions.

The upper and middle lobes of the right lung were enlarged and consolidated. The cut surface of these lobes was uniformly grayish red and only slightly moist. The lower lobe of the right lung and the left lung showed no changes. The hilar lymph nodes on the right were enlarged, moist and hyperemic; those on the left were natural.

The pericardial sac contained about 30 to 40 cc. of greenish yellow, moderately thick pus, containing shreds of fibrin. The visceral and parietal layers appeared thick, dull and shaggy as they were separated. The heart was normal in size and showed no pathologic changes.

The other organs showed no significant pathologic changes.

Microscopic Observations.—Whole lobe sections revealed a variegated picture in the upper and middle lobes of the right lung. The bronchi were swollen, almost uniformly; they contained an exudate of polymorphonuclear leukocytes, desquamated epithelial cells, amorphous debris and nuclear fragments. Their walls were thickened by dense accumulations of histiocytes, plasma cells and lymphocytes. These were found in the subepithelial tissue and between the muscle fibers as well; they surrounded the bronchi and bronchioles in coronal fashion.

In some bronchial branches metaplasia of the epithelium to the squamous variety was found. In these areas polymorphonuclear leukocytes were seen migrating through the epithelium.

The alveoli were the seat of a confluent inflammatory process. Near the apex of the upper lobe of the right lung this process was patchy in distribution, and there was moderate collapse. The majority of affected lobules contained a fairly uniform fibrinopurulent exudate. Occasional alveoli showed large numbers of large mononuclear cells with abundant deeply staining eosinophilic cytoplasm.

Near the hilus in both lobes there were lobules showing a different change (fig. 9). In these the alveoli were smaller than normal and lined by tall columnar epithelium. They contained moderate numbers of foamy macrophages and many epithelioid monocytes with deeply eosinophilic cytoplasm. In sections stained with hematoxylin and eosin there were numbers of large multinucleated giant cells in many alveoli. Some exhibited one or two vacuoles, usually spherical in outline.

Toward the base of each lobe there was a severe interstitial inflammatory process which had conspicuously thickened the interlobular and interalveolar septums and diminished the size of the air spaces. The cells included large numbers of plasma

cells, lymphocytes, lipophages and histiocytes. Fibroblasts and increased strands of collagenous connective tissue were also demonstrable.

In the lower lobe of the right lung there were several sublobular areas of productive inflammatory reaction in the interstitial tissue. The left lung was normal except for focal peribronchial histiocytic infiltration, the presence of a few foamy macrophages in the hilar lobules and fresh fibrinous pleuritis.

The pleura over the affected lobes exhibited fresh fibrinous exudate, while the interlobular septums, except at the bases, showed edema and prominent lymphatics distended with polymorphonuclear leukocytes, but no vacuolated macrophages were evident.

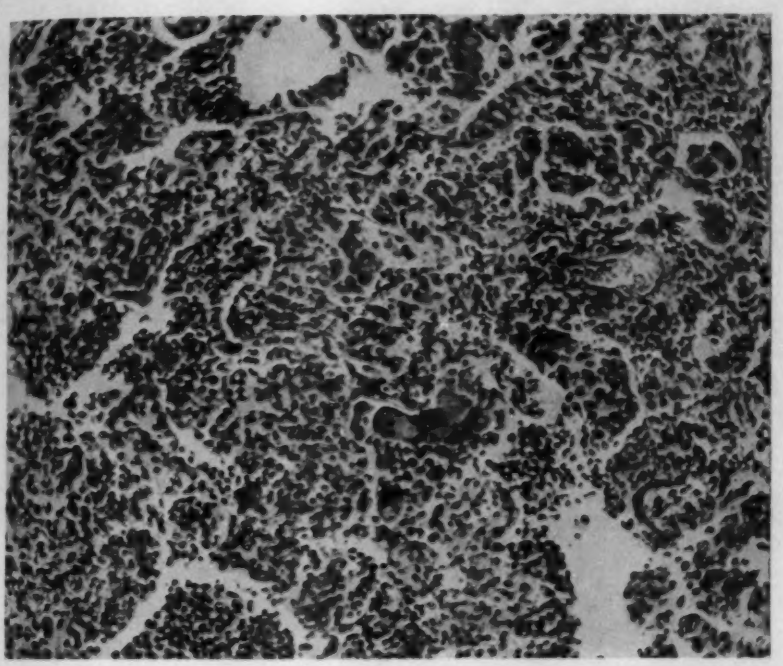

Fig. 9 (case 7).—Photomicrograph of a paraffin section of the upper lobe of the right lung. The alveoli are filled with epithelioid monocytes, and there are a number of foreign body giant cells with smooth nonvacuolated cytoplasm (hematoxylin and eosin). See figure 10.

Frozen sections stained with sudan IV revealed fine sudanophilic droplets in the foamy macrophages and in the histiocytes in the interstitial tissue. Osmic acid preparations revealed similar intracellular lipids; in addition, in sections from all parts of the upper and middle lobes many air sacs showed shreddy masses of material which had precipitated the osmic acid.

Because of the numbers of epithelioid monocytes and multinucleated giant cells with few vacuoles, Ziehl-Neelsen stains were done on paraffin and frozen sections to demonstrate tubercle bacilli. They revealed, scattered throughout the affected lobules, varying numbers and sizes of acid-fast droplets, both intracellular and extra-

cellular. They were seen (fig. 10) as solid droplets, as ring forms rimming vacuoles and as a purplish red granular material in the monocytes, in the foreign body giant cells and in the fibrinopurulent exudate. None were seen within polymorphonuclear leukocytes.

Nile blue sulfate stains demonstrated little free neutral fat or fatty acid material. It stained the intracellular and extracellular lipid dark blue.

Polariscopic examination disclosed no doubly refractile material, even after heating and cooling.

Fig. 10 (case 7).—Drawing of a multinucleated giant cell found in the consolidated lung shown in figure 9, after staining with carbolfuchsin. The acid-fast shreds, droplets and ring forms are shown in the cytoplasm. A macrophage (appearing as an epithelioid cell when stained with hematoxylin and eosin) is shown stuffed with acid-fast granules. Its nucleus is seen at the upper edge of the cell. The same material dissolved sudan IV.

Histologic sections of the other organs exhibited no relevant changes.

Final Diagnosis.—The diagnosis was chronic interstitial broncholobular pneumonia with aspiration of cod liver oil and lipid reaction in the right lung, acute diffuse lobular (pneumococcic) pneumonia of the right upper and middle lobes, bilateral acute fibrinous pleuritis and acute fibrinopurulent pericarditis.

When the foreign body giant cells and epithelioid monocytes were first encountered in ordinary paraffin sections, the presence of a foreign lipid was not considered. Sections were stained with carbolfuchsin for tubercle bacilli, and intracellular droplets and granules of acid-fast material were found. To what extent the acute inflammatory reaction was due to the presence of the oil cannot be determined. The finding of the type XIV pneumococcus in the sputum, the homogeneous lobar consolidation and the characteristic clinical course make it certain that the acute reaction in the lung was in part due to the pneumococcus. Sudan IV and nile blue sulfate stains revealed much masked lipid (see table 3 for the staining reactions noted). It should be noted that sections passed through the ordinary lipid solvents showed no vacuoles (indicative of soluble lipid) within the many monocytes lying in the alveoli and interstitial tissue. The finding of widespread interstitial infiltration and some fibrosis suggested pneumonitis prior to the acute fibrinopurulent reaction. In cases 5 and 6 the lesions may have been somewhat less advanced than those in case 7, because there was less interstitial fibrosis. But if this feature was independent of the lipid reaction, one cannot estimate the age of the process.

Lipid extraction and analysis were done in this case (table 2), and the results support the conclusion that only small amounts of oil were aspirated. The total amount is attributable to the presence of saponifiable lipid, and the iodine value is like that found in case 4 and higher than any obtained in lipid extracts from the normal lung.

In cases 5 and 6 there were areas of necrosis and beginning abscess formation, and since the acid-fast material and oil were concentrated in these areas, it seems likely that oil produced the necrosis. However, if gastric juice was aspirated with the oil, necrosis might have been due to this material.

CONFIRMATORY STUDIES

Drs. Paul Cannon,[15] Kano Ikeda[16] and Murray Angevine[17] have enabled me to confirm the observations described in this series by a study of tissue or slides in cases of lipid pneumonia due to aspiration of cod liver oil reported by them.

Dr. Cannon's case is particularly instructive, for it illustrates the aspiration of cod liver oil by a healthy infant during forced feeding.

A boy 5 months old entered the hospital because of cough and fever of five weeks' duration. Roentgenograms revealed several cavities in the right lung, and there were signs of bronchopneumonia of the upper lobe of the right lung. The parents stated that the symptoms appeared after the first administration of cod liver oil. Ten minims (0.6 cc.) was given by medicine dropper with the child on his

15. Cannon, P.: Arch. Path. **19**:135, 1935.
16. Ikeda, K.: Am. J. Dis. Child. **49**:985, 1935.
17. Baumgartner, L., and Angevine, M.: Am. J. M. Sc. **192**:252, 1936.

back. Soon forced feeding became necessary to continue the treatment. The parents gave as many as five doses at a time before the child could be made to swallow one; on two occasions they held his nose, after he had already coughed and choked when the oil was given. Necropsy revealed pneumonia in the right lung, focal pleuritis, peritonitis and suppurative otitis media. Microscopic examination showed desquamative pneumonia, free lipid in the alveolar spaces and only moderate numbers of polymorphonuclear leukocytes. The abscess cavities were filled with lipid, amorphous debris and leukocytes and were surrounded by granulation tissue containing occasional giant cells. The pieces of tissue sent to me were embedded in paraffin, and Ziehl-Neelsen preparations revealed a concentration of acid-fast membranes and lipid, both extracellular and intracellular, within the abscess cavities and their walls (fig. 11).

Fig. 11.—Low power photomicrograph of a section from the lesion observed in Dr. Cannon's case, showing the acid-fast material as black membranes and rings and masses. In the center the alveolar walls had been destroyed (carbolfuchsin and methylene blue).

The material lent by Dr. Angevine and Dr. Ikeda shows in both cases a process belonging in the group of advanced or proliferative pneumonitis associated with aspiration of cod liver oil. In both cases the slides show a tendency toward granuloma formation and proliferation of the interstitial histiocytes of the alveolar septums. Multinucleated

giant cells and macrophages were present and contained particles and globules of the oil which were uniformly invested by acid-fast membranes; only traces of extracellular lipid were found, and these were acid-fast too.

To make certain that the acid-fast membranes regularly form around cod liver oil and halibut liver oil when these are introduced into the tissues, experimental studies [18] of the tissue reaction were undertaken, with cod liver oil, halibut liver oil and a variety of other oils. In the experiments with cod liver oil 19 animals were used (16 monkeys and 3 rabbits), and in each animal the oil was introduced into the lung by transtracheal injection; in 10 animals it was injected subcutaneously, intramuscularly and intraperitoneally. In all these animals sterile cod liver oil produced an acute inflammatory seropurulent or fibrinopurulent reaction (fig. 7) within twenty-four hours, while an acid-fast membrane appeared on the surface of the oil as early as three hours after injection. These features persisted for several weeks. The acute inflammation disappeared when the oil and acid-fast membranes were phagocytosed or encapsulated (fig. 12).

The nature of the acid-fast membrane encountered in the reaction to cod liver oil is not clear. Pinkerton [4] first noted it in experiments with the oil and likened it to the film which forms on oil drying through exposure to the air. He expressed the opinion that a film of oxidized oil formed on the globules in the lungs and that this was an insoluble altered oil. As a result of the studies made in the cases tabulated in this paper as well as in the experiments, I came to another conclusion. Stains for fibrin showed that the membrane contained precipitated protein—probably fibrin—from the beginning of its formation. Experiments in vitro have shown that when cod liver oil is layered over serum or plasma a similar membrane is visible at the oil-serum or oil-plasma interface after thirty minutes. Like the histologic membrane,[19] it increases in density with time, contracts and becomes

18. Graef, I.; Kaufmann, W., and Kaplan, L.: Arch. Path. **26**:914, 1938.

19. While this paper was in preparation, Hass reported on the tissue reaction to various fractions of cod liver oil which he prepared (Arch. Path. **26**:956, 1938). He, as Pinkerton and as my associates and I did, noted the development of acid-fast membranes around cod liver oil after injection of the oil into the subcutaneous tissue. He discussed the formation of the membrane and noted an increase in its density with time. As we did, he found formation of large amounts of acid-fast material around injected acid fractions of cod liver oil. He further showed that the esters of saturated fractions did not yield insoluble acid-fast material and that the amount of the membrane formed in the zone of injection in any of the applications of the esters is the function of the boiling point of the ester employed. He found that the increase in the amount of insoluble material and acid-fast material in the zone of reaction may be positively correlated with the average unsaturation

(Footnote continued on next page)

puckered. This has been observed in hanging drop preparations and in sealed capillary tubes as well. Oil is bound in this membrane quite tenaciously, and prolonged sojourn in the normal fat solvents does not liberate it. On observing this condition, my associates and I were led to see whether or not lipid could be demonstrated in our paraffin sections, and by staining ordinary deparaffinized sections with sudan IV and mounting them in gelatin or glycerin we found it in the acid-fast membranes.

The histologic reaction in chronic conditions is essentially a foreign body reaction to the membrane, but fibrosis is not conspicuous around

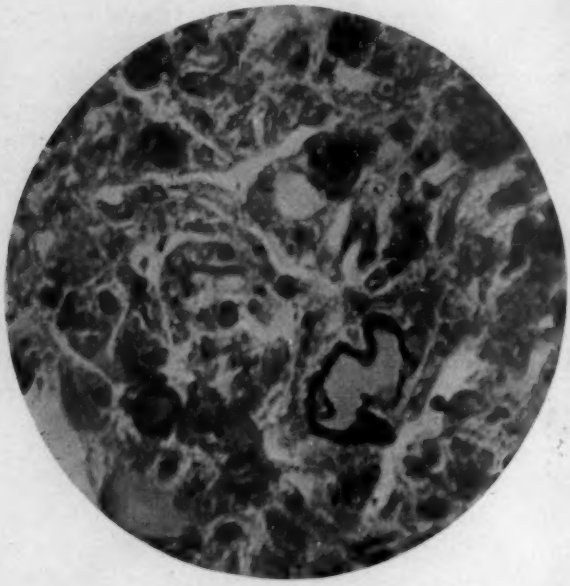

Fig. 12.—Granulomatous nodule in the mesentery of a monkey six months after an intraperitoneal injection of cod liver oil. Droplets of oil surrounded by dense acid-fast membranes or solid acid-fast granules are enclosed by multinucleated or mononuclear macrophages (carbolfuchsin and methylene blue).

the oil or lipoprotein membranes. Interstitial fibrosis was seen in 2 instances but not around oil or membranes per se; this is in contrast to the reaction to liquid petrolatum.

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of the compounds and fractions employed. In unpublished experiments, using hydrogenated cod liver oil furnished by Mead Johnson & Co., we found that hydrogenation of the oil prevents formation of an acid-fast membrane. It should be pointed out that the observations in Hass's experiments began at one week after injection, and the promptness with which the acid-fast membrane forms on contact with body fluids was overlooked.

It is important to note that the interfacial membranes mask the presence of the lipid. Unless the odor of the oil is detected at necropsy [20] or there is clinical suspicion, the true irritant may be overlooked, for the gross appearance is not distinctive, although a greasy surface may be exposed on section. Even histologic preparations require special care, since vacuolated macrophages were relatively scanty. In 1 case the macrophages looked like epithelioid monocytes. In the cases in which foreign body giant cells were noted, one or two vacuoles were seen in the cytoplasm of these foreign body giant cells, but most of the cells looked like the ordinary Langhans type, with smooth acidophilic cytoplasm in hematoxylin-eosin preparations. Free and bound oil may be seen within the membranes by using lipid stains on frozen sections.

It is noteworthy that the oil was not identified in the hilar lymph nodes in any of the cases studied. However, when the membrane-covered droplets are finally phagocytosed, the macrophages may carry them to the lymphatics. This has been observed in chronic experiments.

The acute inflammatory reaction [21] to cod liver oil bespeaks its irritating powers. Furthermore, the oil is apparently not disposed of until the acid-fast membrane forms around it and phagocytosis follows. For no oil or fragments of acid-fast membrane were seen in the polymorphonuclear leukocytes at any time, and large amounts of extracellular oil were demonstrable within the membranes in frozen sections. When very small amounts of oil are aspirated, the membrane may form very quickly, and phagocytosis follows.

The chemical extractions in this series of cases of lipid pneumonia due to aspiration of cod liver oil were limited to cases 4 and 7. It is interesting that the iodine values determined on the total lipid in these 2 cases were almost identical. Fresh cod liver oil has an iodine value in the neighborhood of 150, but oxidation and partial saturation of the fatty acids in this oil must take place with a sojourn in body fluids and exposure to the action of oxygen. Tests of the effect of 10 per cent formaldehyde showed only slight reduction in the iodine value of cod liver oil.

20. As in the case described by Dr. Angevine.

21. Pinkerton in his experiments with cod liver oil studied one animal eighteen hours after the injection of the oil and others fifteen, twenty-one, thirty-eight, fifty and one hundred and ten days after the injection. It is not surprising that he and Paterson (who studied experimental lesions seven, twenty-seven and thirty days after the injection of cod liver oil [J. Path. & Bact. **46**:151, 1938]) should have overlooked the early inflammatory response to the oil. Paterson appears to have overlooked the formation of acid-fast membranes around cod liver oil altogether. It is worth emphasizing that there is an absence of lipophages in the earliest stages of the reaction.

The aspiration of cod liver oil into human lungs must be attributed to accident in the majority of instances. It is interesting that in this series aspiration of the oil was not suspected on clinical grounds. Five patients presented a clinical picture of severe pneumonia with high fever, and 1 of the remaining 2 was considered to have bronchopneumonia; in the case of the other no pulmonary diagnosis was made. The results of roentgenographic examinations were available on 4 patients, and the roentgenograms of 2 of these, in whom lobar consolidation was present, showed increased density in the affected fields. In 1 instance in which acid-fast membranes and staining reactions were considered to support the diagnosis of aspiration of cod liver oil there was no record of the child's having received cod liver oil. Nevertheless, it seemed wiser to include this case in this series, because of the distinctive histologic reaction. In this case viosterol had been used clinically, but experimental studies of the reaction to viosterol showed that no acid-fast membranes were formed on it.

Forced feeding, especially when accompanied by holding of the nose (which compels violent inspiration), regurgitation of ingested oil with gastric contents or the administration of large amounts of oil to very small, feeble or comatose infants may readily lead to aspiration of oil into the lung. Probably the administration of oil should be avoided altogether if the patient has difficulty with deglutition or a palatal defect, and the danger of aspiration should deter one from forced feeding. The small dose required in the use of vitamin concentrates offers a substitute by which aspiration pneumonia may be avoided.

SUMMARY

A study of 7 cases of pneumonitis revealed the presence in the lungs of free or intracellular lipid, considered to be cod liver oil, with a characteristic histologic reaction. Around the oil there was conspicuous formation of a hyaline membrane which was acidophilic and acid-fast (resistant to decolorization in acid alcohol). In advanced lesions phagocytosis was observed, with persistence of the lipid as acid-fast material within macrophages. The earliest response to the presence of cod liver oil in the lungs is an exudate composed of plasma, polymorphonuclear leukocytes and few mononuclear cells. This persists until the oil is encapsulated by acid-fast membranes or fibers.

Sudan IV and nile blue sulfate stains when applied to deparaffinized sections showed that the membrane is in part an insoluble lipid. Phosphotungstic acid–hematoxylin staining revealed shreds or fibers of fibrin within the membranes. Similar membranes were produced experimentally in monkeys and rabbits. Dense acid-fast membranes were formed in vitro by layering cod liver oil and halibut liver oil over plasma or serum. The membrane therefore appears to be the product

of interfacial activity in a lipid-aqueous system (containing mixed proteins). Tentatively it may be designated as a lipoprotein which acts like a foreign body in the tissues. Chemical extraction for lipids in 2 cases confirmed the interpretation that an exogenous lipid of the nature of a semidrying oil was present in the lungs.

The aspiration of cod liver oil in man may accompany forced feeding, regurgitation, repeated vomiting or difficult deglutition. By the use of very small doses or the substitution of concentrated preparations containing the desired vitamins one may avoid the harmful effects of the aspiration of cod or halibut liver oil.

Confirmation of these findings was obtained by the study of 3 additional cases from other sources. In all these cases the lipid was surrounded by acid-fast membranes.

II. LIPID PNEUMONIA DUE TO LIQUID PETROLATUM

The vast majority of published reports ascribe lipid pneumonia to the aspiration of liquid petrolatum. The early studies by Laughlen [8] and Pinkerton [22] indicated that this substance is removed from the lungs with difficulty. The latter showed that the oil could be identified readily by the simple histochemical procedure of fixing or staining the suspected tissue with osmic acid. Since the oil readily dissolves sudan IV and does not reduce osmic acid as vegetable and animal oils or fats do, it can be detected even when other lipids are present. He also showed that liquid petrolatum is quickly emulsified and attracts large numbers of macrophages and that at the same time it induces a fibroblastic reaction.

Many of the reports of lipid pneumonia do not offer sufficient evidence to prove that an exogenous lipid was present. Clinical reports of value are those which emphasize an adequate history, persistent characteristic roentgen evidence and the finding of lipophages in the sputum. Some reports are based on roentgenographic and clinical information only. Others include postmortem studies, but many of these do not offer histochemical evidence to implicate liquid petrolatum, cod liver oil or other lipids. The reports by Pinkerton [2] are admirable for thorough histochemical study, and the reports by Baumgartner and Angevine,[17] Houck,[10] Klinck [11] and Fetterman [23] and those of some of the cases observed by Ikeda [8] and Hayes and Gardner [24] contain sufficient evidence to enable one to identify the lipid responsible. Since lipophages may be present in conventional purulent pneumonia or in chronic pulmonary suppuration, it is essential that the involved pulmonic tissue

22. Pinkerton.[2,4]
23. Fetterman, G. H.: J. Lab. & Clin. Med. **22**:619, 1937.
24. Hayes, J. N., and Gardner, L.: Tr. Am. Clin. & Climat. A. **59**:192, 1934.

be histochemically examined with the purpose of identifying the suspected lipid. A differential study of the lipid is desirable, furthermore, because many different oils or fats are used in the oral administration of drugs or foods as well as in nasal medication.

Ikeda [8] observed two types of reactions following aspiration of liquid petrolatum. From his experience and a review of reported cases, he separated lesions into infantile and adult forms. In the former the characteristic findings were a diffuse outpouring of macrophages and slight diffuse interstitial fibrosis. In the adult forms the resemblance to a paraffinoma is complete with the finding of nodular granulomatous lesions varying from macroscopic nodules to massive infiltrations indistinguishable from neoplasms or tuberculous foci on roentgen or on superficial gross examination.

My experience does not wholly support this separation of the lesions according to the ages of the patients, for I have found the granulomatous nodular lesions in children and the diffuse exudative lesions in adults. It is true that such lesions are often only incidental in adults, while they may be the chief pathologic feature in infants.

Liquid petrolatum in the tissues in these cases was identified by finding that the globules dissolved sudan IV but failed to reduce osmic acid. The specificity of this reaction was supported by lipid extraction in this series.

Tables 4 to 8 summarize the findings among 6 infants and 9 adults in whose lungs lipid lesions were encountered.

GROUP 1. ACUTE LESIONS IN INFANTS

Among the children there were 3 (table 4, cases 8, 9 and 10), 5½, 6 weeks and 1 year of age, respectively, with fresh pneumonic consolidation. The presence of lipid was not anticipated clinically or on gross examination. Histologic study of paraffin sections and of frozen sections stained differentially showed a diffuse alveolar exudate of foamy (lipid-containing) macrophages. The lipid failed to reduce osmic acid, barely stained pink with nile blue sulfate and was orange-yellow with sudan IV. It was therefore considered to be liquid petrolatum.[25] There was focal suppuration in the lungs of 2 of the infants, but the chief lesion was the macrophagic exudate throughout the lower lobes and in the central regions of all lobes. No free, extracellular oil was found in frozen sections. Stains for acid-fast material were negative.

For 1 child (case 10) there was a clinical record of forced feeding of liquid petrolatum on two occasions during the first two weeks of

25. These chemical reactions have been noted by Pinkerton and others. They have been verified in experimental studies.

a six weeks' stay in the hospital. For the other 2 patients no history of the use of any lipid was obtainable, and the conclusion that liquid petrolatum was responsible was based on histochemical examination. However, there was a record of respiratory difficulty following regurgitation in 1 infant; in the other, a premature infant, occasional regurgitation may have played the same role in the aspiration of oil.

TABLE 4.—*Lipid Pneumonia in Infants Due to Recent Aspiration of Liquid Petrolatum*

	Case 8	Case 9	Case 10
Age	5½ weeks	6 weeks	1 year
Clinical diagnosis	Pyopneumothorax; otitis media	Prematurity; malnutrition	Bronchopneumonia; cleft palate; pterygium colli
Hospital stay	2 days	1 day	6 weeks
Fever	104 F.	103 F.	High terminally
Roentgen examination	Shadow at base of left lung	Not done	Increased bronchial markings
Pulmonary signs	Cyanosis and dyspnea	None noted	Cyanosis six days
Other clinical observations	History of coughing after belching 2 days before admission	History of gavage feedings; occasional vomiting	Forced feeding of liquid petrolatum three times
Lipid, dose and administration	Not ascertained	Viosterol, 5 drops daily 3 weeks, by mouth	Liquid petrolatum, 15-30 cc., during first two weeks, by mouth
Pathologic pulmonary changes	Lobular consolidation in lower lobe of left lung; pyopneumothorax on left, with collapse of lower lobe of left lung	Congestion and edema; purulent bronchitis	Lobular pneumonia, confluent, in upper and lower lobes of right and left lungs
Microscopic changes	1. Diffuse lobular exudate of oil-laden macrophages 2. Focal purulent lobular pneumonia 3. Fibrinopurulent pleuritis	1. Focal and confluent lobular exudate of oil-filled macrophages	1. Confluent and focal lobular exudate of foamy macrophages containing oil 2. Purulent lobular pneumonia upper lobe of right lung
Histochemical examination			
Sudan IV	Orange-yellow	Orange	Orange-yellow
Nile blue sulfate	0	0	Most globules 0, some faintly pink
Osmic acid	0	0	0
Ziehl-Neelsen*	0	0	0
Polariscopic	0	0	0
Other pathologic conditions	Acute fibrinous pericarditis and mediastinitis; postmortem lung culture gave Staph. aureus	Erosions of esophagus; hemorrhagic gastritis; otitis media	Internal hydrocephalus; pterygium colli

* This stain was used in determining the presence of acid-fast material.

The clinical study of these patients resulted in the diagnosis of pneumonia in 2 (cases 8 and 10); the third was moribund on admission. In case 8 signs of pneumonia developed in a 6 week old well baby following marked gaseous eructation and coughing, and the baby died two days later. In case 10 the child was hospitalized with pterygium colli and mild internal hydrocephalus, and received forced feedings of liquid petrolatum.

Staphylococcus aureus was found in cultures from the focal suppurative lesions in case 8; no cultures were made in the other cases. Fever was noted in cases 8 and 10, but was absent in the case of the premature infant. Case 10 is presented in detail to illustrate this group because in this case the data are most abundant.

Case 10.—J. W. was readmitted to the hospital at the age of 10 months with hydrocephalus, mongolism, aural discharge and pterygium colli. At 7 weeks of age he had suppurative otitis media, and at 2 months, unexplained high fever with convulsions. After improvement a recurrence of otitis media and fever was noted, and he was readmitted seven weeks before death.

Examination on readmission revealed a disproportionately large head and a purulent discharge from the ears. There was no fever for the first five weeks; then low grade fever developed and persisted without other signs for the next fourteen days; during the last four days the temperature rose to 105 F. Ten days before death signs of dehydration and acidosis developed, as well as a cough. Roentgen examination revealed "increased bronchial markings on the right." Two days before death the lungs were full of coarse, moist rales. Bronchial breathing, dulness and resonant rales were found medial to the scapulas on both sides, and a clinical diagnosis of broncholobular pneumonia was made. Death followed increasing respiratory distress.

Six days after admission ½ ounce (15 cc.) of liquid petrolatum had been forcibly administered by mouth; 1 ounce (30 cc.) was given subsequently on two occasions. There was no record of forcing at the latter feedings, and no other lipids were administered. These feedings could not be correlated with any respiratory distress.

Significant Postmortem Observations.—There was marked emaciation. The head was disproportionately large. The pleural sacs were free from exudate or adhesions, and the lining was smooth everywhere. The lungs were crepitant except in patches of purplish consolidation, present in both upper and lower lobes. On section the consolidated zones corresponded to the lobular markings and were yellowish gray or reddish purple. The trachea, bronchi and pulmonary vessels were natural; the hilar lymph nodes were not enlarged. Examination of the brain revealed slight internal hydrocephalus. The other organs showed nothing significant.

Microscopic Observations on Whole Lobe Sections.—The hilar lobules of the upper and lower lobes of the left lung were the seat of a peculiar exudate, which more or less filled the alveolar space (fig. 13). It was fairly uniform and consisted of a mass of foamy macrophages with huge vacuoles in their cytoplasm. Some were arranged in a pseudosyncytial manner so that their cytoplasmic boundaries could not be made out. In some alveoli a fine fibrinous or albuminous matrix enmeshed the macrophages. The alveolar walls were prominent and their capillaries engorged, and the lining epithelium was slightly swollen. The same exudate was found in the lumens of some bronchioles. Polymorphonuclear leukocytes were notably scanty and widely scattered. The interlobular septums, blood vessels and major bronchi showed no significant changes.

Sections of the right lung showed more marked and confluent consolidation of the upper lobe with a similar exudate, and in places the exudate was frankly purulent. Scattered lobules in the lower lobe exhibited the same lesion. In the middle lobe patchy involvement was seen, which was marked in the hilar lobules. Peribronchial lymphoid follicles were also prominent because of edema

and hyperemia in this section, but contained no lipophages. The hilar lymph nodes were hyperplastic and exhibited red blood cells in their cortical sinuses. The pleura on both sides as well as the interlobular connective tissue and the blood vessels were normal.

Lipid stains showed soluble lipid within the foamy macrophages. Rarely a lipophage was seen in the interlobular septums. The lipid globules within cells failed to reduce osmic acid, suggesting the presence of liquid petrolatum. They also failed to stain with nile blue sulfate, confirming the impression that this lipid was neither a vegetable nor an animal lipid. With sudan IV the lipid was salmon pink. Some additional lipid, which was extracellular, reduced osmic acid and gave a blue reaction with nile blue sulfate. It was considered, there-

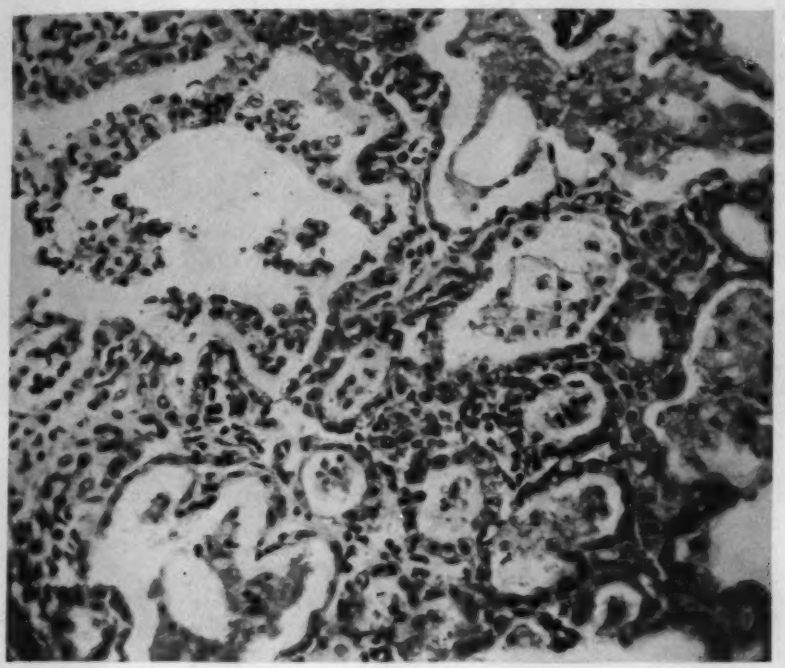

Fig. 13 (case 10).—Acute lipid pneumonia due to liquid petrolatum mixed with another irritant. Some alveoli are full of foamy lipophages, and others contain polymorphonuclear leukocytes and debris as well. Note the swollen lining epithelium and the focal interstitial infiltration by monocytes.

fore, to be of a different nature from the nonreactive oil found only within macrophages. Since no other oil had been administered, it was considered to be milk fat.

Final Diagnosis.—The diagnosis was acute lipid pneumonia due to the aspiration of liquid petrolatum, and acute purulent lobular pneumonia of the upper lobe of the right lung.

This and the other 2 cases in this group show that the early response following aspiration of liquid petrolatum is a distinctive outpouring of macrophages, which engulf the finely divided oil and accumulate in the alveoli.

In very young or feeble infants the aspiration of liquid petrolatum alone, like that of cod liver oil, may lead to asphyxial pneumonia unaccompanied by fever. Ikeda [8] observed this too. In some instances it is likely that organisms are aspirated with the oil, and the conventional purulent inflammation may obscure the presence of the lipid until microscopic examination is done.

TABLE 5.—*Chronic Lipid Pneumonia in Children Due to Aspiration of Liquid Petrolatum*

	Case 11	Case 12	Case 13
Age	6½ months	18 months	5½ years
Clinical diagnosis	Chronic lobular pneumonia; acute otitis media	Chronic "lipoid" pneumonia; rickets	Acute glomerulonephritis with uremia; bronchitis; otitis media
Hospital stay	22 days	1½ years	2 days
Fever	Intermittent	Intermittent	None
Pulmonary signs	Signs of consolidation in right lung; hyperpnea	Pneumonia at 4 and 7 months and signs over right lung thereafter (see text)	None
Roentgen examination	Persistent shadow in upper lobe of right lung since age of 2 weeks	Persistent shadow in right lung 11 months	Not done
Other clinical observations	Recurrent infection of upper respiratory tract since birth	See text	Pneumonia at 2 years; frequent colds
Lipid, dose and administration	Albolene "nose drops" irregularly since first month	Albolene "nose drops" twice daily; amount ? cod liver oil, 2 cc., by mouth intermittently	Not ascertained
Pathologic pulmonary changes	Confluent lobular consolidation in upper and lower lobes of right lung and lower lobe of left lung	Confluent lobular consolidation in both lungs—gray on section	Congestion and edema
Microscopic changes	1. Confluent fibrinopurulent pneumonia 2. Alveolar and interstitial deposit of foamy macrophages containing oil 3. Traces of free lipid in alveoli	1. Marked interstitial and intra-alveolar deposit of oil in macrophages 2. Focal fibrinopurulent exudate in bronchioles	1. Patchy sublobular, peribronchial and endobronchial lipid granulomas 2. Focal subpleural fibrosis 3. Few oil-filled macrophages in hilar lymph nodes
Histochemical examination			
Sudan IV	Yellow	Yellow-pink	Orange-yellow
Nile blue sulfate	Pale pink	0	Most globules 0—some light pink
Osmic acid	0	0	Almost all globules—0
Ziehl-Neelsen	0	0	0
Polariscopic	0	0	0
Other pathologic conditions	Acute otitis media	Rickets; malnutrition	Acute diffuse glomerulonephritis; generalized edema

GROUP 2. CHRONIC LESIONS IN INFANTS

The chronic inflammatory changes following aspiration of liquid petrolatum were shown in a group of children (table 5, cases 11, 12 and 13). They correspond to those in many similar cases recorded in

the literature. In both cases 11 and 12 there was widespread alveolar and interstitial accumulation of macrophages filled with oil globules, and in both this appeared to have followed prolonged use of "nose drops." Case 11 was that of an infant who was recalled as having had curious recurrent respiratory signs and persistent roentgen shadows in the right upper pulmonary field. On reviewing the case, a jar with pulmonary tissue, stored for several years, was opened, and free oil was seen floating on the surface. Histochemical examination of pulmonary sections, as well as chemical analysis, showed it to be liquid petrolatum.

The findings in case 12 are given in detail because the lesions are striking examples of the diffuse interstitial pneumonitis which may follow aspiration of liquid petrolatum. Chemical analysis was done on several samples of tissue and confirmed the histochemical evidence of this oil (table 6).

CASE 12.—J. F., a boy, died at the age of 18 months in Bellevue Hospital. He had been a patient there most of his life. He weighed 5 pounds 7 ounces (2,495 Gm.) at birth and breathed badly. For weeks feeding had to be forced or given by gavage, and there were many periods of vomiting. He had recurrent infections of the ear and persistent nasopharyngitis; for the latter, nasal instillations of ephedrine in oil and neo-silvol were used intermittently for a period of seven months. He was fed evaporated milk mixtures for two and one half months, then a Czerny-Kleinschmidt formula (rich in butter fat); cod liver oil and liquid petrolatum were also given by mouth from time to time. At 3 months of age he had acute pneumonia and otitis media lasting six weeks; another attack at 5 months lasted about four weeks. From the age of 8 months until death at 18 months he was practically never free from fever, leukocytosis or signs of consolidation. Respirations were always rapid after the first attack of pneumonia (rate 40 to 100).

Roentgenograms showed at first diffuse consolidation on the right side; later, hilar shadows persisted. They were mottled (fig. 14) and conspicuous on the right side. In one attack of pneumonia a pneumococcus (type XIV) was found in the sputum. The body weight never exceeded 11 pounds (4,989.5 Gm.). The Mantoux test was repeatedly negative. The clinical diagnosis of "lipoid pneumonia" was made, and death occurred during a recurrent bout of fever with continued signs of pneumonia.

Significant Observations at Autopsy.—The body was that of a markedly undernourished and underdeveloped infant. Examination was limited to a thoracic incision and study of the lungs. The pleural sacs were free from fluid. Both lungs were voluminous, and the right lung was adherent to the wall of the chest laterally and posteriorly by adhesions, which were broken with slight difficulty. The right lung (fig. 15) was large and retained its shape when placed on the table. The posterior half of the upper lobe was firm, and this region presented a striking yellow-gray color, visible through the pleura. The septal markings were prominent, and the lobules were readily visualized. The anterior half of the upper lobe was not consolidated, but crepitus was markedly diminished, and here and there was a rubbery resistance. The middle lobe showed a small patch of consolidation near the hilus, and on section resembled the posterior portion of the upper lobe. The lower lobe showed in its posterior two thirds the same

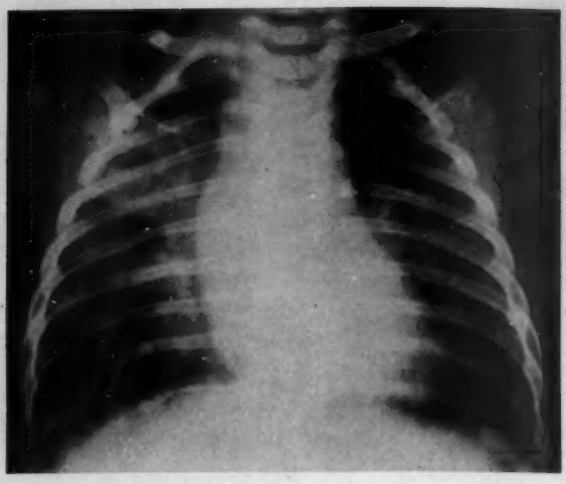

Fig. 14 (case 12).—Shadows in the right lung field around the hilus and in the upper lobe, and to a lesser extent in the hilus of the left lung field of an infant aged 18 months. These shadows persisted for many months.

Fig. 15 (case 12).—Photograph of the cut surface of a section of the right lung, showing diffuse consolidation of both the upper and the lower lobe. Note the smooth, shiny pleura.

prominently lobulated infiltration, visible through the pleura. The cut surfaces were firm, dry and not greasy. The anterior portion of this lobe of the lung was pink and somewhat crepitant.

The left lung showed the same appearance in the posterior third of each lobe. The anterior two thirds of both lobes was gray and showed prominent lobular

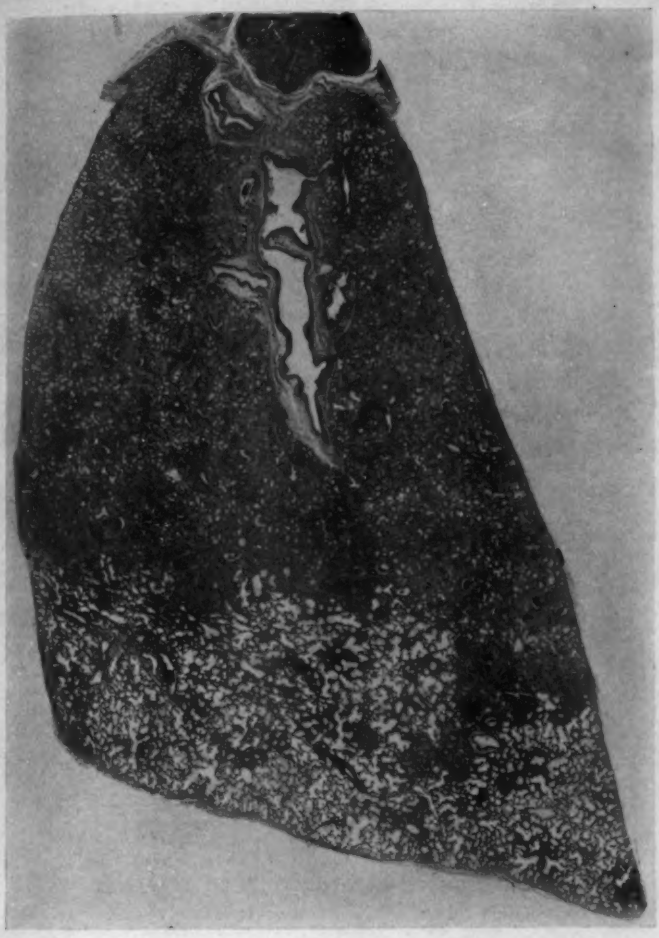

Fig. 16 (case 12).—Whole lobe section of the middle lobe of the right lung. The hilar three fourths of this lobe is apparently consolidated. See figure 17.

markings with occasional patches of yellow consolidation. The paratracheal and peribronchial lymph nodes were slightly enlarged and discrete.

Microscopic Observations.—Much of each lung was poorly expanded or consolidated (fig. 16). The most striking observation was the extensive proportions attained by the interstitium, which appeared to be converted into adipose tissue, so that few alveoli remained per field (figs. 17 and 18). The remains of many

alveoli were identified by dilated atriums, and these too contained foamy lipophages. Reticulum stains (fig. 19) revealed a diffuse increase in reticulum fibers surrounding each interstitially placed lipophage. In places there was a patchy alveolar exudate of foamy mononuclear cells and polymorphonuclear cells. Some alveoli which were relatively normal contained a few foamy macrophages (fig. 20).

The alveolar and the bronchiolar epithelium were predominantly fetal in type. Many bronchioles were dilated and contained an exudate of polymorphonu-

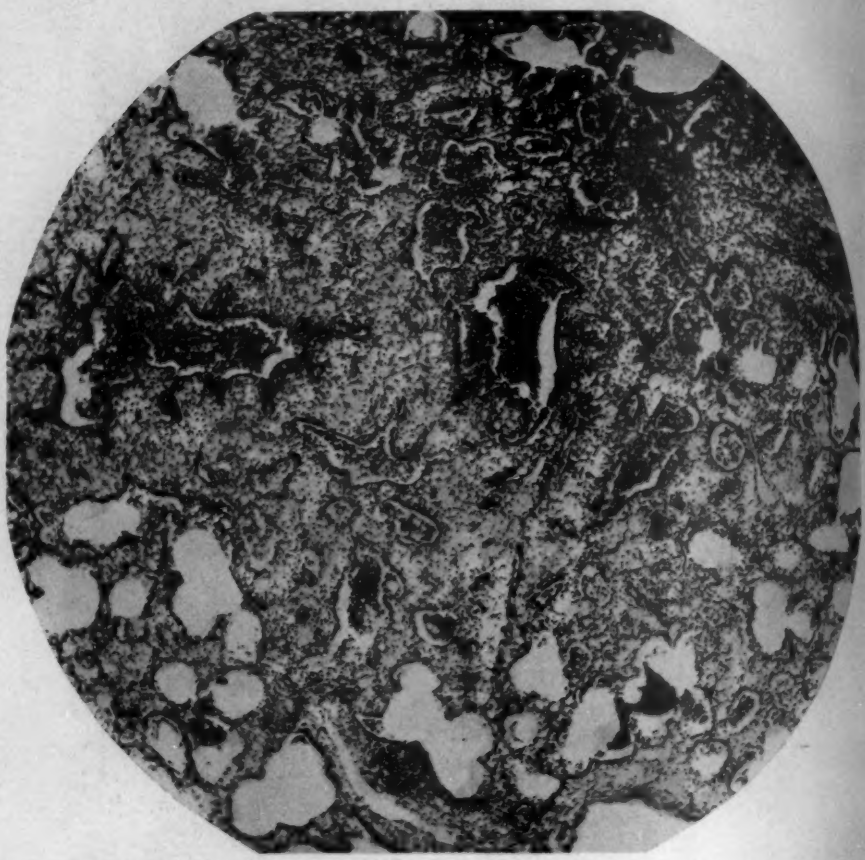

Fig. 17 (case 12).—This photomicrograph shows how the lung is converted into tissue resembling fat. The persistent atria contain leukocytes and are lined by cuboidal or columnar epithelium.

clear leukocytes, foamy mononuclear cells and fibrin. A few exhibited mural infiltration by similar cells. There were no vascular lesions, lymphangitis or fresh pleuritis.

In frozen sections the vacuoles were shown to contain liquid petrolatum by their failure to reduce osmic acid, by the bright yellow color obtained when sudan III was applied and by the absence of anisotropic material. All the lipid was intracellular. The hilar lymph nodes contained a few lipophages in their sinuses.

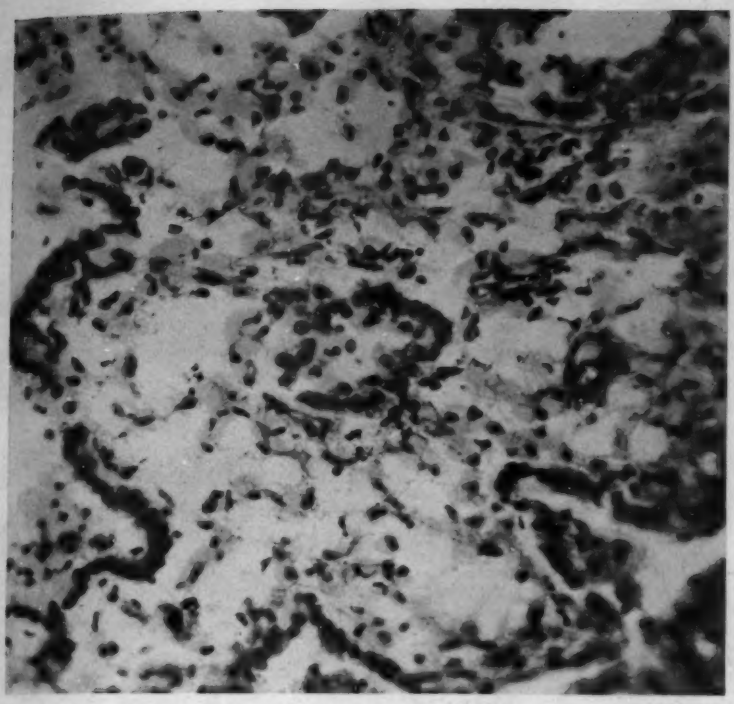

Fig. 18 (case 12).—Highly magnified field in a section of the lower lobe of the right lung, which shows the interstitial deposit of highly vacuolated lipophages. Note that the epithelium of the few persisting sacs is columnar and that its cells are free from vacuoles.

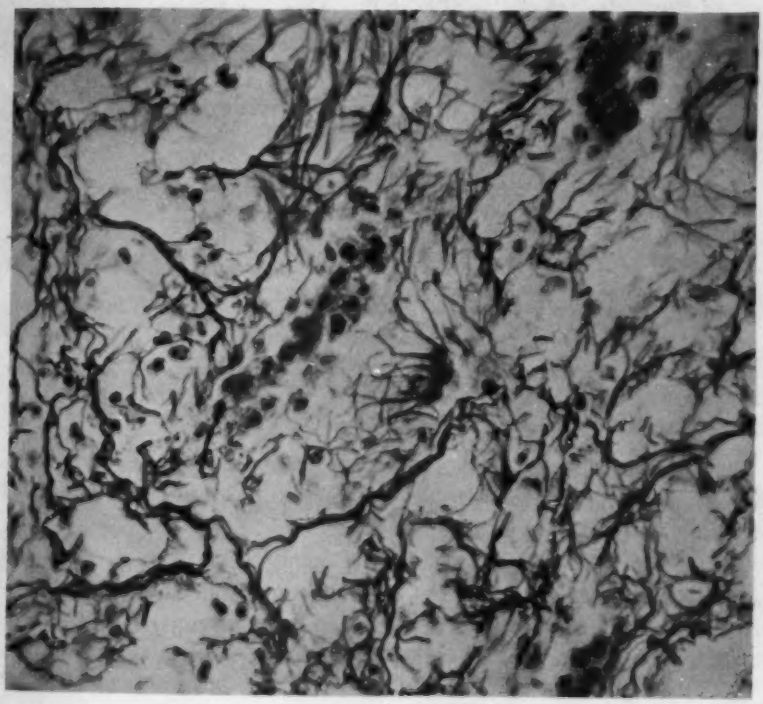

Fig. 19.—A field from the same block shown in figure 6. The section was stained for reticulum by the method of Foot and Foot. The nuclei of the individual macrophages are dimly outlined; the epithelial clusters are shown by the darkly staining nuclei. Note the diffuse reticulum formation.

No anisotropic material was demonstrated on polariscopic examination. No acid-fast material was found in sections stained by the Ziehl-Neelsen method.

Chemical Analyses.—Table 6 records analyses of three different samples of lung without regard to the degree of visible consolidation. The first, a dry sample weighing 3.26 Gm., yielded 0.871 Gm. (26.7 per cent) of total lipid; of this, 0.686 Gm. represented the total unsaponifiable portion (20.9 per cent of the total sample and 78.7 per cent of the total lipid). The cholesterol yields in the latter two analyses were within normal limits, being 0.1 per cent and 0.18 per cent, respectively.

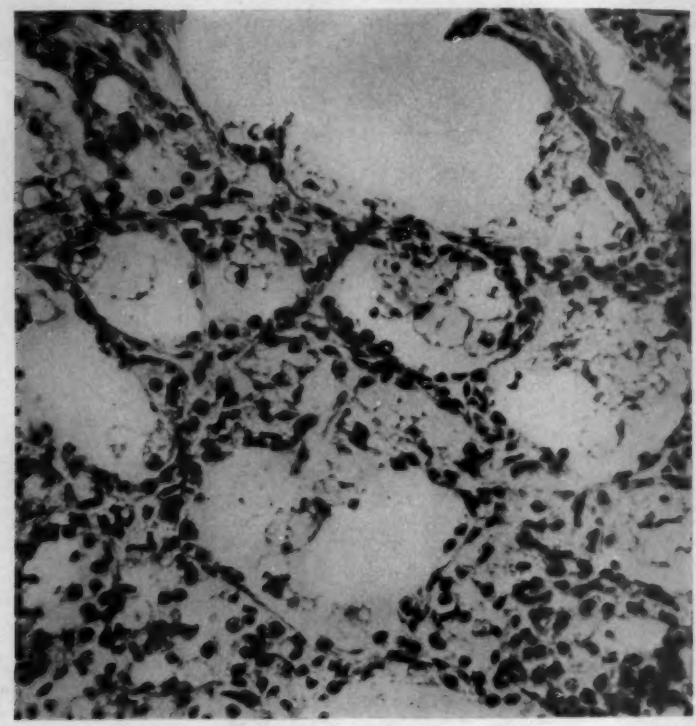

Fig. 20 (case 12).—Oil-filled macrophages are shown lying free in the alveoli.

Final Diagnosis.—The diagnosis was chronic lipid pneumonia due to liquid petrolatum, suppurative endobronchitis and endobronchiolitis, chronic bronchitis, patchy emphysema and collapse.

The histochemical reactions and the chemical analyses in this case showed that liquid petrolatum was present in large amounts and intimately associated with the lesions found. Histologic examination demonstrated that this material was phagocytosed by macrophages, which transported the material to the interstitial tissues. There it accumulated chiefly in the form of intracellular oil and produced diffuse fibrosis, as demonstrated by reticulum stains.

TABLE 6.—*Results of Analyses for Lipid in Five Cases of Pneumonia Associated with the Aspiration of Liquid Petrolatum*

Case	Lipid Implicated	Sample: Wet Weight, Gm.	Sample: Dry Weight, Gm.	Total Lipid, Gm.*	Percentage of Dry Weight	Total Saponifiable Lipid, Gm.	Percentage of Total Lipid	Total Unsaponifiable Lipid, Gm.	Percentage of Total Lipid	Iodine Value on Total Lipid	Cholesterol, Gm.	Percentage of Cholesterol in Unsaponifiable Lipid	Percentage of Cholesterol in Total Lipid	Comment
12.....	Liquid petrolatum	.....	3.26	0.882+	27	0.187	21	0.684	77	Not done	0.004 to 0.011	1	1.6	Colorless oil recovered after alcohol-ether extraction
15 "Normal" part.	Liquid petrolatum	5.515	3.969	0.072	18.1	0.016	23	0.058	80.6	2.9	0.00067	11.6	0 9	Light yellow oil obtained after alcohol-ether extraction
15 Pneumonic part	Liquid petrolatum	4.455	..... 0.458	0.352 0.440	76.8 96 0	0.020 0.022	4.5 5.0	0.312 0.350	88.6 79.6	5.1 4.4	0.00080 0.00042	4.6 2.4	0.23 0.09	of pneumonic portion
16.....	Liquid petrolatum	6.8 12.3	1.15 0.7236	1.28 1.178	112 162	0.132 0.10	10 8	1.11 1.02	86 87	5.36 5.84	..... 0.013	? 1.3	... 1.1	Light yellow oil recovered after alcohol-ether extraction
19.....	Liquid petrolatum	13.2	1.95	0.351	17.5	.....	..	0.250	71	18.89	0.013	6.2	3.7	Light yellow oil
22.....	Liquid petrolatum	.....	14	1.97	14 †	.....	..	1.43	70	...	0.021	14	...	Light yellow o'l

* From 2 to 3 per cent of wet normal lung washed free from blood and mucus may be lipid; this is 10 to 16 per cent when calculated from the dry weight (Pincussen, in Oppenheimer, C.: Handbuch der Biochemie des Menschen und der Tiere, Jena, Gustav Fischer, 1909-1913, vol. 4, p. 289). In cases 19 and 22 only focal lesions were found, which accounts for the relatively low total lipid. However, most of it was unsaponifiable oil. In case 12 the total lipid was not determined originally, and the figures shown represent the sum of the saponifiable, unsaponifiable and cholesterol fractions, and the percental fractions thereafter are based on this calculated total.

† The dry weight was not recorded.

The clinical record of vomiting, forced feeding and use of nasal instillations of oil indicates that there was ample opportunity for aspiration of liquid petrolatum and other substances. Since cod liver oil and milk fat were administered by mouth and were not found in the lung, and liquid petrolatum was administered both by mouth and in the form of "nose drops," it seems reasonable to conclude that the oil gained entrance into the larynx and trachea when introduced intranasally.

In both this case and the others there was the characteristic localization of aspirated oil in the posterior dependent portions of the lung and in the perihilar regions.

The histologic picture is consistent with the changes produced when liquid petrolatum is introduced experimentally into the respiratory passages. The emulsification and dispersion in fine droplets seem to permit phagocytosis only by macrophages. The presence of polymorphonuclear leukocytes in the remaining alveolar spaces and bronchioles is most likely part of an independent infectious process, since the oil exhibits no tropism [26] for polymorphonuclear leukocytes. The scanty amount of oil found in the hilar lymph nodes deserves special mention. It suggests that once the oil accumulates in the interstitial lymphatics and around the blood vessels it is not transported further. Moreover, its accumulation may block lymphatic drainage. It is interesting to see how a reticulum is formed around the individual lipophages in the interstitial tissue. If this forms in the lymphatic vessels, it may account for the failure of many of the cells to reach the hilar nodes. More massive scarring probably depends on the continuous laying down of reticulum as long as the oil persists. This is illustrated in case 13 and in some of the cases of chronic lesions in adults.

In case 13 there occurred a wide variety of microscopic lesions which were entirely unsuspected in life and were apparently due to liquid petrolatum. Indeed, repeated studies of ordinary paraffin sections of the lungs failed to yield a satisfactory diagnosis. On review, and after some experience with lipid reactions, certain features suggested histochemical study for lipid, and the results proved the presence of an exogenous lipid. The lesions were varied, and their true nature was recognizable in frozen sections. Some lobules showed miliary interstitial pneumonia in diffuse, fairly even thickening of the alveolar walls by young connective tissue and a few flattened, oil-containing macrophages. Others contained microscopic nodules composed of lymphoid tissue (fig. 21). In paraffin sections the centers of the nodules exhibited large circular spaces, occasionally bound on one side by a thin, apparently compressed strand of eosinophilic protoplasm—sometimes sickle

26. Mudd, S.; McCutcheon, M., and Lucké, B.: Physiol. Rev. **14**:210, 1934.

shaped, sometimes semilunar (fig. 21 *A*). With care, compressed dense chromatin material could be seen at one pole or edge of this light eosinophilic strand. At first glance the nodules appeared to be simply lymphoid follicles, but their irregular distribution in lobules bore no relation to bronchial vessels, bronchioles or pleura. Sometimes two or three were found in a single lobule. Other findings were occasional oil-containing granulomas within the lumens of several bronchioles. They were encapsulated and attached to the bronchiolar wall by strands

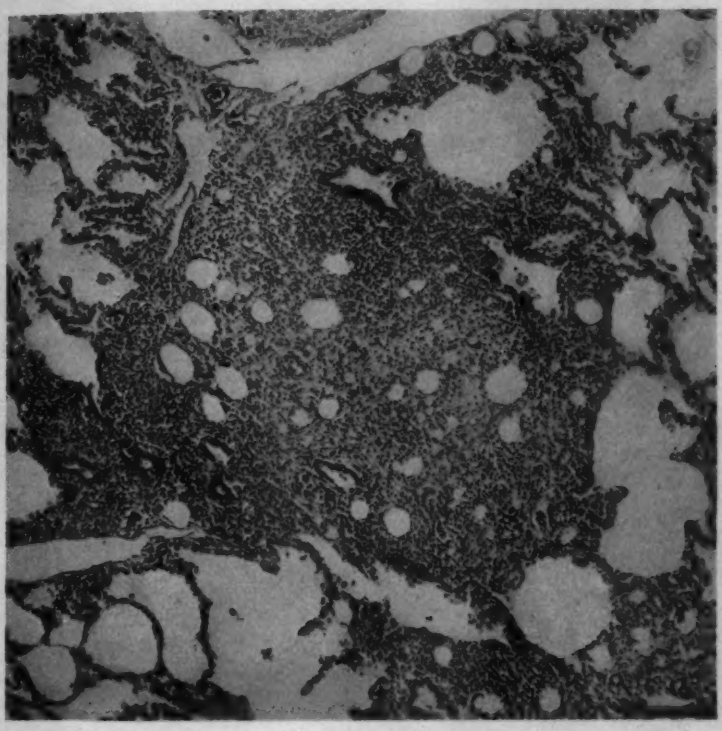

Fig. 21 (case 13).—Photomicrograph showing a well formed lipid granuloma (paraffinoma) observed in the lung of a child 4½ years old. The circular spaces contained sudanophilic lipid which did not precipitate osmic acid.

of young connective tissue. Interlobular septums and some areas of the pleura were also occasionally markedly thickened by connective tissue, and only frozen sections revealed the presence of a few foamy macrophages.

GROUP 3. CHRONIC LESIONS IN ADULTS

Tables 7 and 8 show the pertinent findings in 9 cases in which pneumonitis in adult lungs was attributable to liquid petrolatum. All the lungs exhibited acute and chronic changes in varying degrees.

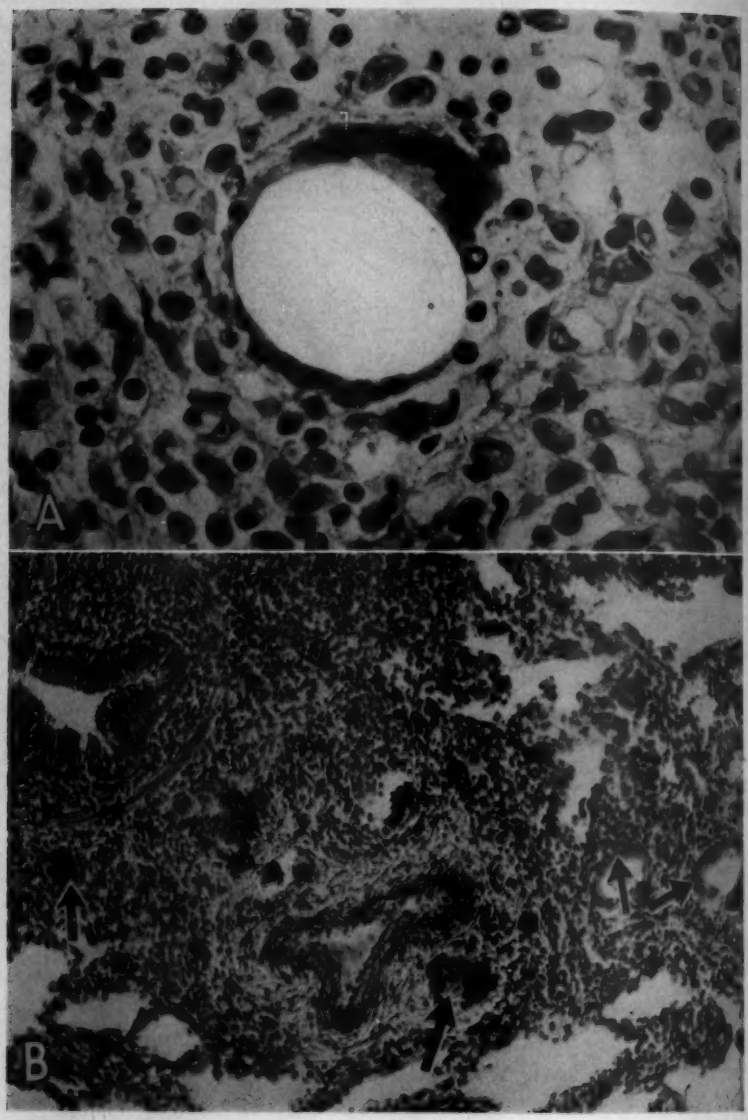

Fig. 22.—*A*, high power photomicrograph showing the details in one of the lipid granulomas shown in figure 21. In the center is a huge multinucleated giant cell containing a large oval space which represents oil dissolved out by the paraffin solvents. A few smaller foamy lipophages are in the tissue around the giant cell together with lymphocytes and a few polymorphonuclear leukocytes.

B, photomicrograph of a frozen section of the lung shown in figure 21. The grayish masses indicated by arrows were stained yellow with sudan IV.

In the first 3 cases (table 7, cases 14, 15 and 16) there was massive consolidation in one or both lower pulmonary lobes; in every case the aspiration of oil appeared to have followed oral administration of liquid

TABLE 7.—*Massive Lipid Pneumonia in Adults Due to Aspiration of Liquid Petrolatum*

	Case 14	Case 15	Case 16
Age	60 years	62 years	65 years
Clinical diagnosis	Cardiospasm and chronic aspiration pneumonia	Early carcinoma of larynx; aspiration pneumonia	Hypertensive and rheumatic heart disease; tetraplegia
Hospital stay	3 months	3 weeks	2 days
Fever	Irregular, low grade	Irregular	104 F.
Pulmonary signs	Irregular signs of consolidation and exudation in both lungs 3 months	Signs of consolidation in lower lobes of both lungs 3 weeks	Signs of consolidation over lower lobe of right lung
Roentgen examination	Persistent hazy shadows at bases of lungs and in upper lobe of left lung	Persistent mottled shadows in lower lobes of lungs	None
Other clinical observations	No history of vomiting	Mass removed from larynx 2 months before death; difficulty in swallowing after radiation therapy	Aphasic and hemiplegic for 2 years and bedridden
Lipid, dose and administration	Liquid petrolatum, 30-90 cc., by mouth 3 times in hospital	Liquid petrolatum by mouth and applied to tongue; ephedrine in liquid petrolatum 1 per cent as "nose drops" 3 times daily	Liquid petrolatum, 30 cc., by mouth daily, at least for duration of hemiplegia
Pathologic pulmonary changes	Irregular focal and confluent lobular pneumonia in lower lobes of both lungs, gray and greasy on section; focal abscesses	Acute fibrinopurulent pleuritis on left; consolidation in lower lobe of left lung; patchy confluent lobular pneumonia in right lung	Consolidation in middle and lower lobes of right and lower lobe of left lung
Microscopic changes	1. Patchy and confluent lobular pneumonia 2. Irregular peribronchial, perivascular and intralobular miliary lipid granulomas 3. Widespread exudate of oil-filled macrophages 4. Actinomycotic abscesses	1. Extensive alveolar exudate of oil-laden macrophages 2. Marked deposit of mucin in same lobules 3. Metaplasia of alveolar epithelium to mucous columnar type 4. Miliary fibrotic lipid granulomas 5. Focal organizing pneumonia 6. Few oil-laden macrophages in hilar lymph nodes	1. Confluent lobular consolidation due to interstitial and intra-alveolar exudate of oil-filled macrophages 2. Traces of free oil 3. Diffuse interstitial fibrosis
Histochemical examination			
Sudan IV	Orange	Yellow to orange	Yellow-orange
Nile blue sulfate	Most globules 0, a few pink	Most globules faintly pink, some 0	0
Osmic acid	Some globules 0, some +	0	0
Ziehl-Neelsen	0	0	0
Polariscopic	Few + droplets	0	0
Other pathologic conditions	Dilatation and hypertrophy of esophagus	Multiple acute gastric ulcers	Hypertrophy and dilatation of heart; healed mitral valvulitis with valvular stenosis and insufficiency

petrolatum. Each case is notable in its own way. In case 14 the patient was a 60 year old man with cardiospasm and massive dilatation of the esophagus. He suffered several attacks of aspiration pneumonia and

TABLE 8.—*Chronic (Focal) Lipid Pneumonia in Adults Due to Aspiration of Liquid Petrolatum*

	Case 17	Case 18	Case 19	Case 20	Case 21	Case 22
Age	41 years	66 years	75 years	76 years	85 years	70 years
Clinical diagnosis	Rheumatic heart disease with congestive heart failure; hemiplegia	Arteriosclerotic heart disease; congestive heart failure; psychosis	Carcinoma of stomach; arteriosclerotic gangrene of left leg; bronchopneumonia	Fractured femur; senility; acute cystitis	Hypertensive heart disease; terminal bronchopneumonia	Death while under anesthesia, after operation for recurrent adamantinoma of jaw
Hospital stay	1 week	24 hours	2½ months	9 months	6 days	14 days
Fever	Slight, terminal	None	Prolonged, intermittent	Low grade 2 months	None	None
Pulmonary signs	Rales at bases	None recorded	Scattered rales and focal changes in breath sounds 1 month	None recorded	Scattered rales	None recorded
Roentgen examination	None	None	Increased peribronchial markings, both lungs	None	None	None
Other clinical observations	Hemiplegic for 10 mo.	Psychosis of unknown duration	Coma for 2 days before death	.....	Tuberculosis diagnosed 30 years ago	
Lipid, dose and administration	Liquid petrolatum, 30 cc., by mouth occasionally	Not determinable	Liquid petrolatum by mouth occasionally	Liquid petrolatum, 30 cc., by mouth occasionally	Not determinable	Liquid petrolatum applied to oral burns after irradiation; dose ?
Pathologic pulmonary changes	Multiple grayish nodules in middle lobe of right and lower lobe of left lung	Focal lobular consolidation in middle and lower lobes of right lung	Focal lobular consolidation chiefly in lower lobes	Confluent and focal lobular pneumonia with reddish gray granular cut surface	Multiple grayish red lobular and smaller zones of consolidation in upper and lower lobes of right lung	Multiple irregular firm grayish nodules (0.1-2 cm.) with pleural scarring, chiefly in lower lobes
Microscopic changes	1. Nodular deposits of oil in macrophages and among fibers of scars 2. Some intra-alveolar foamy macrophages in zones of purulent exudation	1. Interstitial and alveolar deposit of oil entirely within macrophages	1. Focal lobular fibrinopurulent pneumonitis with foamy macrophages and occasional multinucleated giant cells 2. Focal interstitial fibrosis and focal fibroblastic organization of alveolar exudate	1. Irregular interstitial and perivascular fibrosis with alveolar and interstitial infiltration by oil-filled macrophages 2. Focal acute purulent pneumonitis	1. Focal lobular fibrosis with interstitial deposits of oil, intracellular and extracellular 2. Focal purulent lobular pneumonia 3. Oil-filled macrophages in some alveolar sacs, elsewhere mixed with leukocytes	1. All stages in alveolar and interstitial deposition of oil, intracellular and extracellular, and marked fibrosis
Histochemical examination						
Sudan IV	Yellow	Yellow-orange	Yellow-orange	Orange and salmon pink	Orange	Orange
Nile blue sulfate	0	0	Most globules 0, some faint pink	Most globules 0, few faint pink	0	Mostly 0, some light pink globules
Osmic acid	0	0	Most globules 0, occasional + globule	0	Occasional + granule	0
Ziehl-Neelsen	0	0	0	0	0	0
Polariscopic	0	0	0	+	0	0
Other pathologic conditions	Healed mitral valvulitis with stenosis and insufficiency; marked chronic passive congestion; generalized edema	Hypertrophy of heart; coronary sclerosis; syphilitic aortitis; arteriolar nephrosclerosis	Carcinoma of stomach; chronic sphenoidal sinusitis; cerebral arteriosclerosis	Fracture of left femur; acute pyelitis and cystitis	Senility; acute hemorrhagic cystitis	Recurrent adamantinoma of left mandible and tongue

finally died with fresh signs of pneumonia. The pulmonary lesions were quite varied, showing fresh exudative and chronic interstitial or granulomatous forms. In the lower lobes of the lungs there was confluent greasy grayish consolidation involving most of both lobes. Histologically, the diffuse interstitial type of lipid reaction was seen, similar to that found in 2 infants with chronic lipid pneumonia (cases 11 and 12). There were miliary foreign body granulomas as well, with the usual foreign body giant cells or oil-filled macrophages surrounded by young connective tissue and some lymphocytes. A further finding of interest was several small actinomycotic abscesses. The likelihood of aspiration pneumonia was appreciated in the clinical diagnosis.

In case 15 lobar consolidation (fig. 23) was associated with the reaction to aspirated liquid petrolatum, and both acute exudative and

Fig. 23 (case 15).—Massive confluent lobular consolidation in the lower lobe of the left lung. See figure 24.

granulomatous lesions were found. The striking feature in this case, not encountered in any of the others, was the extraordinary amount of mucinous material filling the alveoli and mixed with oil-laden macrophages (fig. 24). Further, the bronchiolar epithelium appeared hyperplastic, and there was pseudometaplasia of the "respiratory epithelium" to ciliated columnar epithelium in many terminal alveoli. This was traced as an extension from hyperplastic bronchiolar epithelium. Focal organizing lesions associated with the oil were also seen in this case.

The condition in case 16 was an example of far advanced diffuse interstitial and alveolar reaction to liquid petrolatum, like that of the infant in case 12. The patient, a cardiac invalid with hemiplegia and aphasia, had been given liquid petrolatum daily by mouth for several years. At her last admission to the hospital there were signs of lobar consolidation over the lower lobes of both lungs. Macroscopically the

lung presented a solid gray appearance in the affected lobes, and the presence of oil was revealed only by microscopic study (fig. 25), confirmed by chemical extraction (table 6).

In the remaining 6 cases (table 8) the focal granulomatous lesions due to the aspiration of liquid petrolatum were observed in aged patients. In these the pulmonary lesions were only incidental findings (fig. 26). Three of the patients had cardiac disease (cases 17, 18 and 21). Two others were bedridden, 1 for gastric carcinoma (case 19) and the second for fracture of a femur (case 20). The sixth patient was an elderly man in good health except for recurrent adamantinoma of the

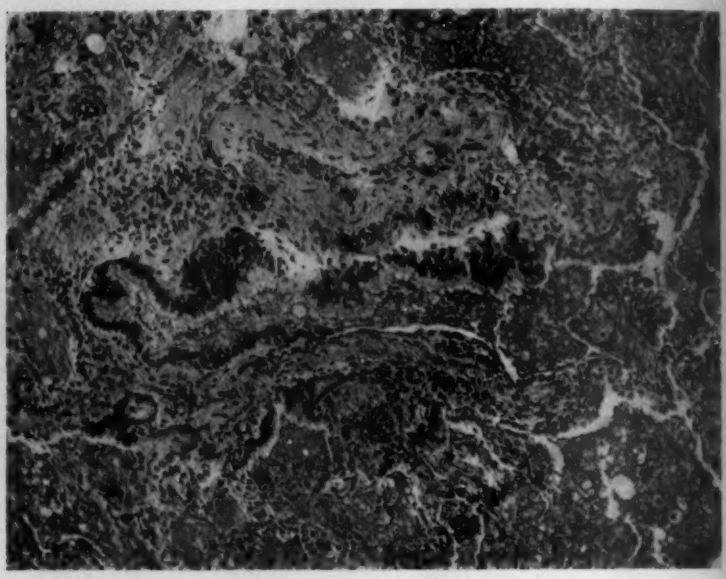

Fig. 24 (case 15).—In this case, in the affected lobules there was an enormous quantity of mucin mixed with oil-containing macrophages. Note the erosion of bronchial epithelium in places and the presence of this tissue on the walls of the sacs behind the bronchi.

jaw (case 22). During radium therapy over a seven year period several oral burns developed, and for treatment of these the patient was advised to hold liquid petrolatum in his mouth. No pulmonary symptoms were recorded in his clinical chart during this period.

The variation in the gross appearance of the lungs in these cases is apparent in the tables. In instances of recent aspiration the presence of oil was not suspected, and in some cases even the consolidation produced was overlooked at the first examination. This was particularly true, also, in the lungs of infants. In the lungs of some of the adults

the affected areas appeared as small, circumscribed fibrous gray nodules, and the presence of oil was not noted in most of them. In a few cases a review of a cross section of the nodules showed glistening oil droplets and a greasy surface on palpation. When the lesions lay close to the pleura, puckering and retraction of the pleura were noted. The resemblance of such nodules to healed tuberculous foci or neoplasms was often striking (fig. 27). In lobes with extensive confluent consolidation

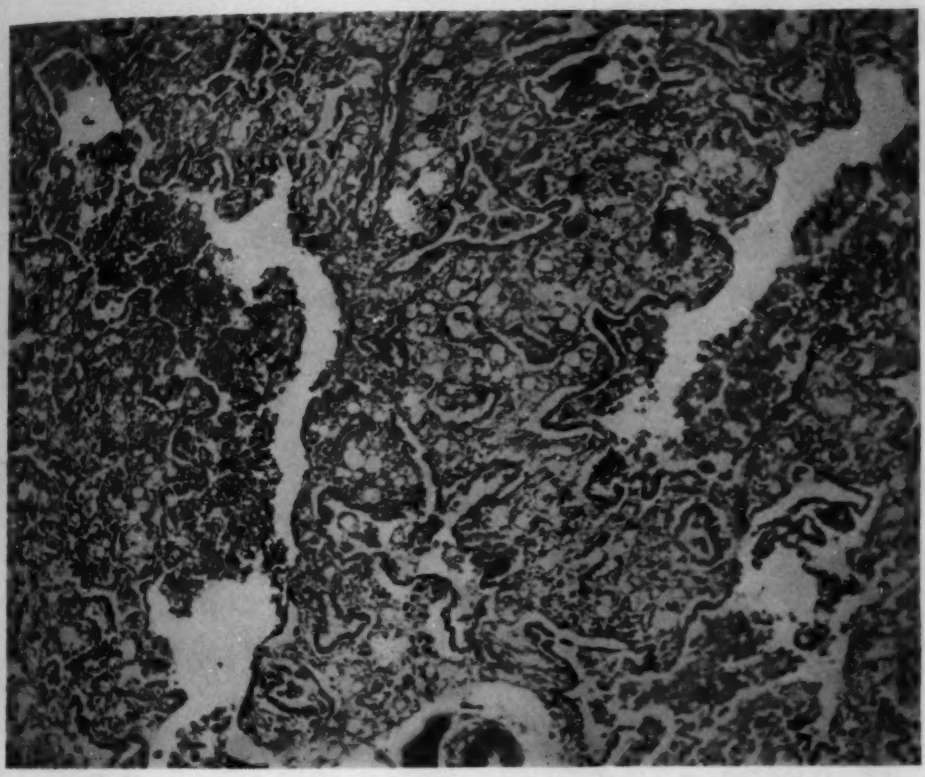

Fig. 25 (case 16).—Diffuse interstitial and alveolar deposits of liquid petrolatum in macrophages. Note the cuboidal or columnar epithelium lining persistent air sacs. The patient had rheumatic heart disease with auricular fibrillation and heart failure, hemiplegia and aphasia of two years' duration. Liquid petrolatum was given by mouth twice daily for two years preceding death.

the presence of oil was unobserved, and the lesions were interpreted as confluent lobular pneumonia in an advanced stage (gray hepatization). In case 14 the greasy nature of the consolidated zones aroused suspicion that oil was present. The color of the affected areas varied from light yellow to gray.

The histologic reaction to liquid petrolatum has been summarized by stating that the oil is rapidly emulsified and phagocytosed by macrophages and that it is apparently eliminated from the lungs with great difficulty. Furthermore, it induces marked fibrous proliferation, tending to fix the deposits. The microscopic lesions varied from lobular or sublobular zones of consolidation to focal granulomatous nodules. In the majority of instances the finding of foamy macrophages in the alveoli drew attention to the presence of the lipid. In the older lesions

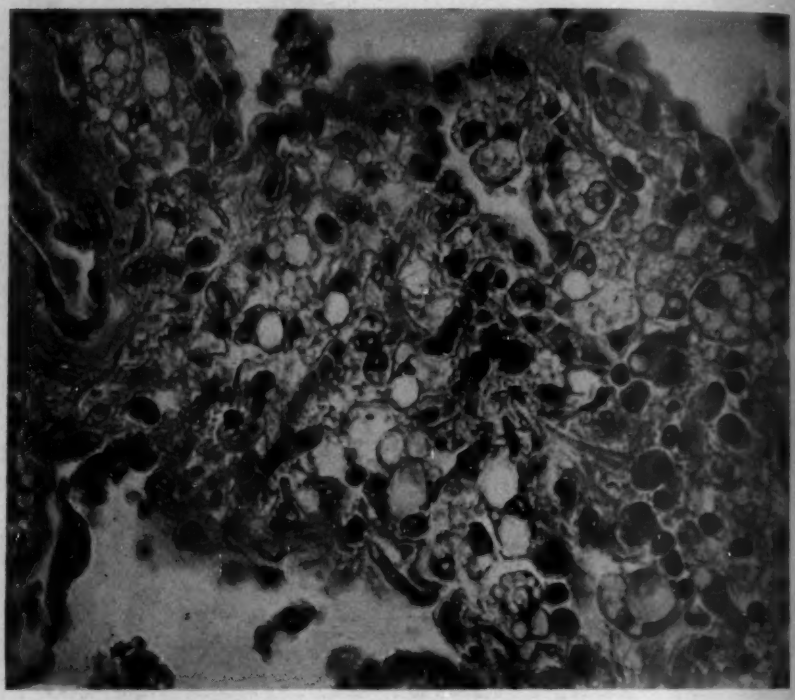

Fig. 26 (case 18).—Focal interstitial deposit of lipophages containing liquid petrolatum, found in patches of consolidation in the lung of an elderly patient who died in heart failure. Note the swollen epithelial cells lining the overlying alveolus.

there were concentrations of liphophages in dense fibrous nodules (fig. 28). While the oil was often found in droplet form in some macrophages, in advanced lesions the drops often coalesced to form huge globules, compressing and displacing the nucleus to one side of the cell. In multinucleated giant cells the globules similarly compressed the nuclei to the periphery. Often the visible cytoplasm and nuclear material were represented by a fine rim which was barely recognizable.

In the early stages of lipid pneumonia due to liquid petrolatum the alveolar epithelium participates by desquamation, and in the chronic forms it exhibits a transformation proportional to the interstitial fibrosis (fig. 25). Where the interstitial deposit of the oil or connective tissue is marked, the adjacent epithelium is likely to be low cuboidal to low columnar epithelium. This reversal to a fetal type of epithelium may

Fig. 27 (case 22).—Multiple nodules of grayish consolidation in the substance of the right lung. Note the puckered pleura overlying some of the nodules. These were mistaken for healed tuberculous scars or neoplastic infiltrations.

reflect the difference in alveolar tension as a result of the interstitial thickening. In no instance was the oil seen within the epithelium. This suggests that it is derived from true epithelium and bears no relation to mesenchymal tissue. In case 15 marked hyperplasia of the bronchiolar epithelium was attended by extension to the infundibular sacs and some

alveoli of the affected lobules. This was accompanied by an extraordinary accumulation of mucinous material in the sacs. It would seem, therefore, that in this type of chronic pneumonitis the presence of the fetal type of epithelium may represent true proliferation of terminal bronchiolar epithelium.

In case 19 the alveoli exhibited an organizing growth of fibroblasts penetrating from one alveolus to another (fig. 29). In case 15 a similar organizing process was part of a much more varied reaction. In the

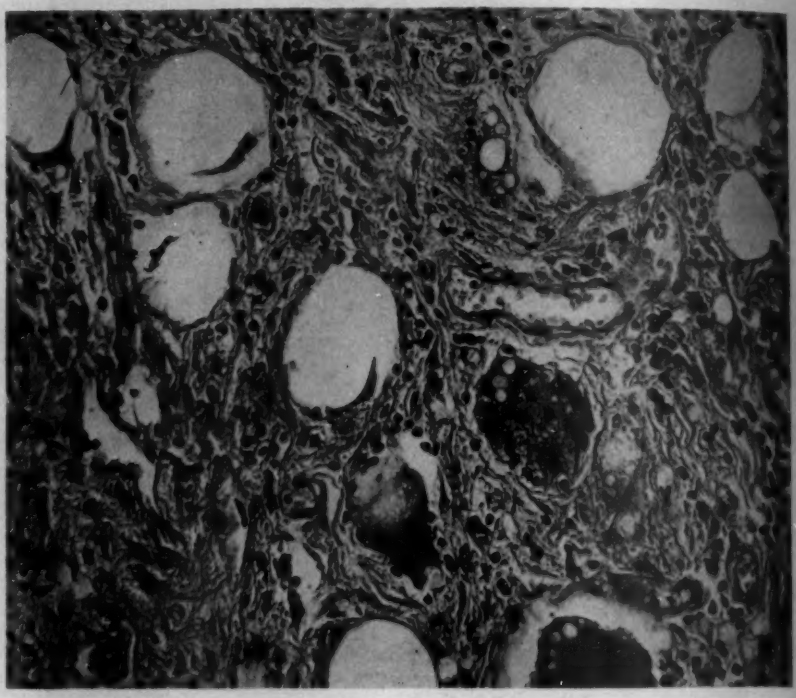

Fig. 28 (case 22).—In some dense scars the oil appeared to be caught between bundles of collagen or as intracellular globules with a thin incomplete rim of cytoplasm and a few compressed nuclei. Other multinucleated giant cells with foamy cytoplasm are also shown. The circular spaces were filled with oil.

meshes of the new connective tissue there were numerous lipophages or oil-containing multinucleated giant cells.

Secondary interstitial reactions were common. A new formation of lymphoid follicles was frequent around small lipid granulomas (fig. 30). These were found in unusual positions within the lobules, their centers often exhibiting a small amount of oil, sometimes appearing like an oversized fat cell with a nucleus compressed at the periphery. In others

the accumulation of lymphocytes was so dense as to mask the presence of the lipid in ordinary paraffin sections. Histiocytic and fibroblastic proliferation within the central walls was common and resulted in diffuse thickening of the alveolar septums and diminution of the air sacs.

It is notable that the oil was rarely found in the hilar lymph nodes of either the adults or the children. Cases 13 and 15 were the only ones in which lipophages were demonstrable in the hilar lymph nodes. Some peribronchial hilar lymph nodes were examined in all the other

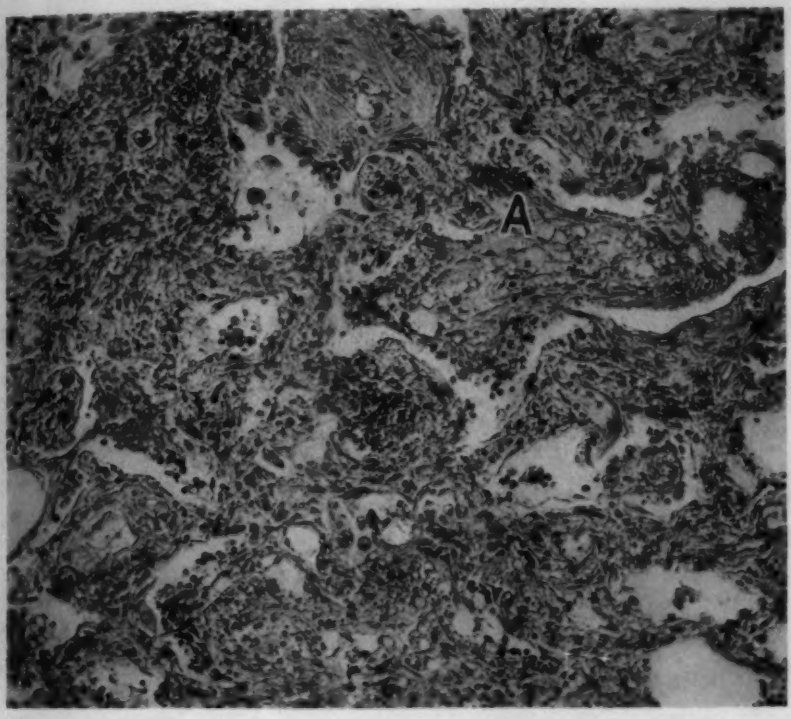

Fig. 29 (case 19).—An organizing type of pneumonitis accompanied the deposit of liquid petrolatum in this case. Intracellular oil is represented by the vacuoles in the macrophages caught in the meshes of connective tissue at *A*.

cases and failed to reveal lipid. In the chronic lesions there was notable accumulation of the oil within cells around blood vessels and bronchi, recalling the accumulation of anthracotic pigment in the same locations. As mentioned before, the accumulation may block lymphatic drainage, especially since a reticulum is formed around the macrophages deposited in the interstitial tissues, and this may limit the further transport of the cells.

In the 6 cases in which focal lesions were encountered in the lungs of adults, the affected lobules in 2 exhibited lipophages mixed with a purulent exudate, and this suggested the probability of a concomitant bacterial infection.

Vascular lesions were encountered in only a single instance in the entire series. They were found in or near the lipid deposits in case 22 and are illustrated in figure 31. The affected vessels exhibited marked narrowing of their lumens as a result of the accumulation of a hyalin-

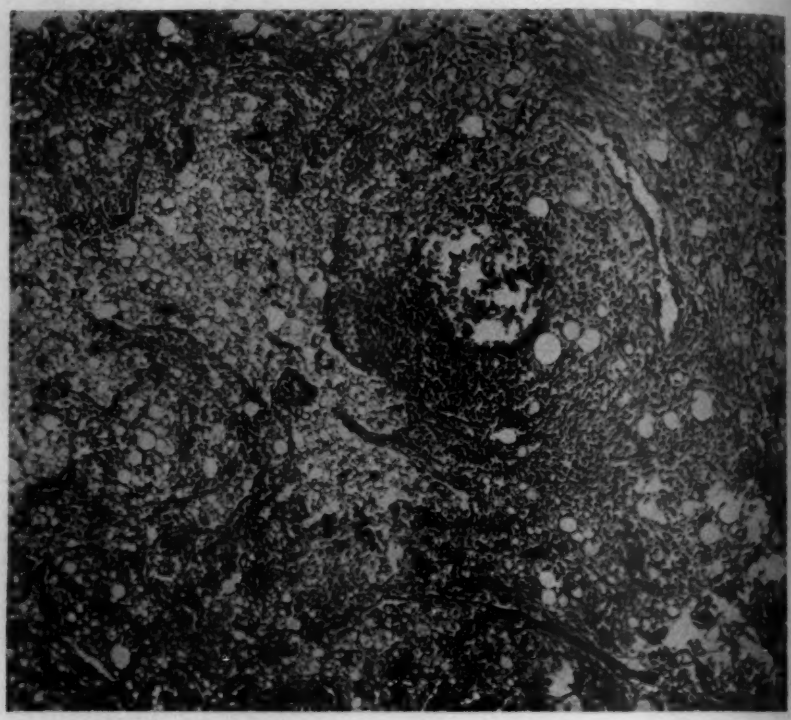

Fig. 30 (case 22).—Note the formation of a lymphoid follicle in an oil-containing scar. In frozen sections the circular spaces are oil filled. Individual lipophages are present in the persistent atrium.

like tissue in the subintimal region. This with appropriate stains appeared to consist of reduplicated elastic lamellae. Some of the vessels appeared to be collapsed and the lumens were virtually obliterated. No lipophages were found in the walls of the vessels. The significance of this vascular lesion was not apparent, nor its precise relation to the surrounding deposit of liquid petrolatum.

It is interesting that in this series no splenic deposits of oil were found, although frozen sections of the spleen were studied with lipid

stains in all cases except case 10 in which permission was obtained for only a limited necropsy. Houck [10] reported finding foreign body giant cells in lymph nodes and in the malpighian bodies of the spleen of a patient with chronic lipid pneumonia of long standing. No other authors have recorded examinations of the spleen with this point in view.

Table 6 comprises the lipid analyses in 5 of the cases in which the pulmonary lesions contained liquid petrolatum. The figures shown in the column following that with the totals of unsaponifiable material indi-

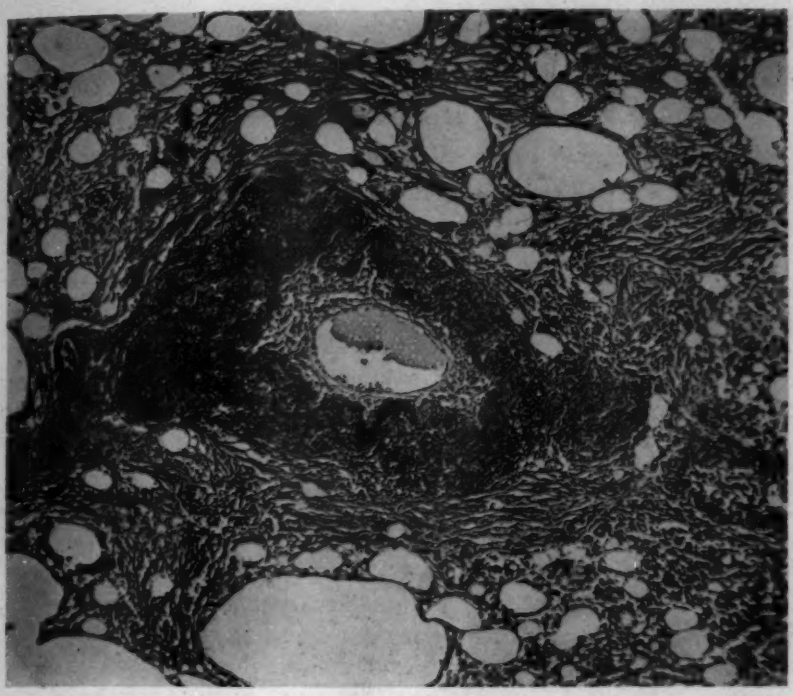

Fig. 31 (case 22).—In some of the scars there is a curious change visible in the walls of the pulmonary arterial branches. In sections stained with hematoxylin and eosin the walls appear smooth and hyalinized, but stains for elastic tissue reveal marked compression and condensation of proliferated elastic tissue. The lumen of the vessel is lined by an irregular layer of young connective tissue containing a few histiocytes and lymphocytes.

cate that in all instances the bulk of the lipid was unsaponifiable and an oil. In 3 cases the lipid absorbed negligible quantities of iodine, further confirming the conclusion that it was chiefly of mineral origin. In this table the total lipid shown as percentage of dry weight of tissue exceeds 100 per cent in two samples (case 16) and is 96 per cent in

another (case 15). Since the lipid was shown to be largely unsaponifiable oil, one can see how saturated the lung may become with this lipid.

The cholesterol content in most instances was within normal limits and 1 per cent or less of the total lipid extracted. Since liquid petrolatum may act as a solvent for other lipids when a mixture is present, some analyses may yield variable contents of saponifiable material or cholesterol and, as would be expected, variable degrees of iodine absorption. The fraction of saponifiable lipid present in the total lipid in these cases varied from 4.5 to 23 per cent. Another source contributing neutral fat or its derivatives may be the endogenous lipid found in associated purulent or suppurative lesions.

COMMENT

Clinically, aspirated oil was considered the cause of pneumonitis in only 2 of the adults in this series (cases 15 and 16), yet the finding of lipid in the lungs of the others leaves no doubt that it was the cause of the pneumonitis in them as well. Debility due to congestive heart failure, malignant tumor and senility, as well as mental or neurologic disturbances or repeated vomiting, may be accountable for interference with the cough reflex and for easy aspiration of nasopharyngeal contents in such cases. Special mention is due cases 15 and 22, in which radiation therapy had been applied to the larynx and buccal mucosa, respectively, for neoplastic involvement. Burns ensued, which were treated by local applications of liquid petrolatum, applied at will by the patients.

Only in cases 14 and 15 and possibly 16, in which the lungs exhibited massive lesions, can the pulmonary alterations be regarded as contributing to the fatal outcome. In cases 14 and 15 there were fresh pneumonitis and suppuration to promote respiratory embarrassment. Whether or not liquid petrolatum alone was being aspirated cannot be stated. Easily recognized, it serves to indicate that aspiration of oil has occurred. In some instances no other agent may be implicated, and the ease with which this oil gains access to the trachea, even in ambulatory patients, is noteworthy. Furthermore, in all the cases reported here in which the lesions were found in adults liquid petrolatum had been administered by mouth; it is possible that some of the patients had used oily "nose drops" as well, but there are no data available on this point.

Roentgenograms were not available in most of these cases, but in cases 14 and 15 repeated roentgen study was reported to have shown persistent signs of consolidation of the lower lobes of both lungs. Of the cases in which children were concerned, roentgenograms were repeatedly made in cases 11 and 12, and in both they showed persistent pulmonary shadows in the right pulmonary field. These findings

correspond with the observations of Goodwin [7] and Pierson [27] among children. Bromer and Wolman,[28] in a recent report based on 23 cases of lipid pneumonia (12 with necropsy), pointed out that the diagnosis can be made by roentgenogram in cases in which there is extensive involvement. It can be based on "the location of the lesions in the perihilar regions in the posterior portions of the lungs, and to a greater degree in the right lung than in the left." All roentgenologic reports stress the need for serial examinations, as well as the unchanging appearance of lesions attributable to liquid petrolatum.

The clinical diagnosis may be aided by bronchoscopic aspiration or by examination of sputum, as in the cases reported by Hayes and Gardner,[24] Houck [10] and Davis [29] and as originally suggested by Pinkerton.[2]

The many reports in the literature and this report show that oil or other free-flowing liquid introduced intranasally or orally may readily gain entrance into the trachea. If there is interference with deglutition, or if there is loss of the cough or gag reflex, forced feeding or the administration of large quantities of oil or of any liquid makes aspiration likely. It may be promoted by certain neurologic states which have in common loss or abolition of the cough reflex. Aspiration of lipids has been found in association with psychotic states, anesthesia, coma and bulbar palsy. It has been noted in association with cleft palate, following gavage feeding or persistent vomiting and after accidental entry of a gavage tube into the trachea. The demonstration of exogenous lipids in the lungs has served to show how easily aspiration may occur in these circumstances and points to the need for extreme care in the administration of any liquids.

Liquid petrolatum was implicated clinically by Ellinger [30] as the cause of persistent pneumonitis in patients following laryngeal operation when it was determined that the oil was used as a lubricant for tracheotomy tubes or for the relief of dryness of throat. It has been shown that habitual use of "nose drops" of liquid petrolatum, especially if in large quantities and over a long period of time, may result in accumulation of this lipid in the lung. Additional danger lies in the aspiration of such oil following its collection in the paranasal sinuses with subsequent discharge into the nasopharynx during sleep.

Cannon and Walsh [31] have thoroughly exposed the dangers of intranasal medication of all sorts in experiments with various laboratory

27. Pierson, J. W.: Am. J. Roentgenol. **27**:572, 1932.
28. Bromer, R. S., and Wolman, I. J.: Radiology **32**:1, 1939.
29. Davis, K. S.: Radiology **26**:131, 1936.
30. Ellinger, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **69**:397, 1934.
31. Cannon, P. R., and Walsh, T. E.: Internat. Clin. **3**:109, 1938.

animals. They showed that oily solutions as well as aqueous solutions when instilled intranasally in small amounts into healthy rabbits went quickly to the lungs. If the solutions aspirated contained living microorganisms, or if the rabbits had snuffles when they received the instillations, the solutions caused severe focal necrosis, purulent pneumonitis and bronchial pneumonia. The observation of Proetz [32] that oily mixtures interfere with ciliary activity by retarding the movement of mucus is pertinent to this discussion and raises the question of the rationale of the therapeutic use of any oil in the respiratory tract. Walsh and Cannon [33] recommended the discontinuance of the use of oils as vehicles for all nasopharyngeal medicaments on the further evidence that drugs dissolved in oil act less effectively than those dissolved in isotonic saline solution. These recommendations should be carefully studied by otorhinolaryngologists. The manufacturers of oily "nose drops" should set a limit to the capacity of the droppers, and the doses for infants and adults should be so adjusted as to prevent accumulation and free flow into the nasopharynx.[34] Substitution of less irritating and more readily absorbable oils would diminish the injury following accidental aspiration. Adequate warning should be given the public against overdosage with any intranasal medication. The use of liquid petrolatum as a lubricant or therapeutic agent in the larynx and trachea should be stopped, in view of the difficulty of removal of this lipid from the lung. The damage caused by the accumulation of even small amounts administered repeatedly over a long period is sufficiently great to warrant the replacement of this oil by other less irritating and more readily removed lipids. There is always the added danger of aspiration of other agents—bacteria, spores or fungi—with any nasopharyngeal liquid.

GENERAL SUMMARY

A study of pneumonic lesions in 15 cases revealed the presence of intracellular lipid considered to be liquid petrolatum, associated with a characteristic histologic reaction. The earliest response to the aspiration of this oil is an outpouring of macrophages, which engulf the finely emulsified oil and accumulate in the alveoli. The aspiration of the oil

32. Proetz, A. W.: Ann. Otol., Rhin. & Laryng. **43**:450, 1934; J. Laryng. & Otol. **49**:447, 1934.

33. Walsh, T. E., and Cannno, P. R.: Ann. Otol., Rhin. & Laryng. **47**:579, 1938.

34. Three droppers from three different commercial preparations of "nose drops" were measured as to capacity. One had a capacity of 2.1 cc.; the second, 1.5 cc., and the third, 1 cc. It is apparent that if the advice of the manufacturer that the person with a cold should instil half a dropperful in each nostril three or four times a day be followed, quantities of 3 to 6 cc. of liquid petrolatum may be introduced in small infants by unsuspecting parents, nurses or physicians.

may be associated with pyogenic infection. In infants it may lead to asphyxial pneumonia.

Macroscopic lesions varied from small pseudotuberculous fibrous scars to lobar consolidation resembling gray hepatization of the lung. Microscopic lesions varied from an acute macrophagic response to dense proliferative scars with imprisoned globules of oil.

Diffuse formation of reticulum and collagen follows phagocytosis of this lipid, and the oil is apparently eliminated from the lungs with the greatest difficulty. The lipophages may accumulate and become fixed in the alveolar walls and gradually diminish the air spaces. Clusters may become encapsulated in small or large paraffinomas, and the fibrosis may produce visible or radiopaque masses. New formation of lymphoid follicles is common around lipid granulomas.

Histochemical examination of the lesions served to identify liquid petrolatum in each instance by its affinity for sudan IV and its failure to precipitate osmic acid.

Chemical extraction in 5 instances yielded large quantities of an unsaponifiable lipid which was a free-flowing oil at room temperature and did not absorb iodine.

In this series aspiration seems to have followed oral or nasal administration of liquid petrolatum. Debility due to congestive heart failure, malignant tumor or senility, mental or neurologic disturbance or repeated vomiting was accountable for interference with the cough reflex and for easy aspiration of nasopharyngeal contents. Two ambulatory patients took liquid petrolatum by mouth for the treatment of oral or laryngeal radium burns.

Roentgenograms were made of 2 children and 1 adult who exhibited recurrent signs of pneumonia in life. These showed persistent pulmonary shadows. The unchanging appearance of lesions attributable to liquid petrolatum and their location around the hilus of the posterior dependent portions of the lung make roentgenologic diagnosis possible.

The dangers of intranasal medication have been stressed, and the particular difficulty presented in the removal of aspirated liquid petrolatum suggests that this oil should not be used in the respiratory tract and that when it is given orally care should be exercised to prevent aspiration of it.

FAT EXCRETION THROUGH THE KIDNEYS

AN EXPERIMENTAL STUDY

CARLO S. SCUDERI, M.D.

CHICAGO

No previous work on the mechanism of the excretion of fat through the kidneys has been recorded in the literature so far as I am able to find. Numerous cases of chylemia have been reported, but the observations recorded have all been purely clinical.

A study of this problem was undertaken because of its relationship to the diagnosis of fat embolism in cases of trauma. Before approaching the problem, it seemed best to determine whether or not normal dogs under varied physiologic conditions ever excrete fat in the urine.

The urine of 2 normal dogs was examined and found to be free from fat by microscopic tests described later. Two dogs which had been given 1 pint (473 cc.) of cream—one three and the other six hours previous to examination of the urine—had no fat in the urine. Two other dogs which were being starved in other experiments also showed no fat in their urine. The kidneys of these 6 animals were sectioned and stained with sudan III. In none was there evidence of fat droplets in either the glomeruli or the tubules.

Since these dogs, under varied physiologic conditions, did not excrete fat in the urine, its presence was considered abnormal.

All the animals in the experiments to be described were operated on under anesthesia induced with pentobarbital sodium.

The pedicle of one kidney was isolated through an incision in the loin and the renal artery carefully dissected from the surrounding tissues. The ureter was then traced to the bladder and cut free, and the end was fitted with a glass cannula. The cannula was brought out through the anterior abdominal wall by way of a stab wound and fixed in place. With a very fine needle fat was injected into the renal artery. When the injection was completed, the renal artery had to be carefully clamped in the longitudinal axis so as to prevent loss of blood through the needle hole and still not completely occlude the renal artery. Occlusion of the artery would result in cessation of the urinary flow from the isolated kidney. For this purpose a miniature paper clip was used, having a small spring in it. After the fat had been injected, the kidney was placed back in the loin, and the wound was sutured.

Both marrow fat from dog bones and olive oil were used in various physical forms. Straight oil or marrow fat was used in some, and emulsified fat in others. As emulsifiers plain water with a little soap and solutions of gardinal

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(a powerful emulsifier) were tried. The results were uniformly the same. In order to increase the urinary output, 200 to 300 cc. of Ringer's solution with 1 Gm. of caffeine or 200 to 250 cc. of 2 per cent urea in physiologic solution of sodium chloride was given intravenously. The urine was collected from the cannula in the anterior abdominal wall and centrifuged at high speed for fifteen minutes. The supernatant liquid was stained with sudan III and examined. A film from the surface of the urine was examined under the microscope for the orange-colored spherical droplets of fat. When present, these varied in diameter from 3 to 8 microns.

TABLE 1.—*Excretion of Fat Through Kidneys in Dogs When Fat Was Injected into the Renal Artery*

Dog*	Weight, Kg.	Amount of Fat Injected	Additional Drugs	Droplets in Urine
3	10.90	1.5 cc. olive oil emulsified, 1.5 cc. soapy water	250 cc. Ringer's solution + 1 Gm. caffeine	4 plus
4	21.8	4 cc. olive oil	300 cc. Ringer's solution + 1 Gm. caffeine	3 plus
5	9.54	1 cc. dog bone marrow fat + 1 cc. pure water, shaken together	300 cc. Ringer's solution + 1 Gm. caffeine	3 plus
6	7.72	3 cc. dog bone marrow fat	200 cc. Ringer's solution + 1 Gm. caffeine	4 plus
17	10.45	2 cc. olive oil	300 cc. saline solution + 1 Gm. caffeine	2 plus
18	8.18	2 cc. olive oil	300 cc. saline solution + 100 cc. 2 per cent urea	4 plus
19	8.18	2 cc. olive oil	300 cc. saline solution + 150 cc. 2 per cent urea	4 plus

* Pentobarbital sodium was used for the production of anesthesia in all the animals.

TABLE 2.—*Excretion of Fat Through Kidneys in Dogs When Fat Was Injected into a Vein of the Leg*

Dog	Weight, Kg.	Amount of Fat Injected, Cc.	Cc. per Kg.	Additional Drugs	Droplets in Urine
20	7.27	10.95	1.5	250 cc. saline solution + 2.5 Gm. urea	2 plus
21	10.8	10.8	1.0	250 cc. saline solution + 2.5 Gm. urea	2 plus
32	11.5	8.6	0.75	250 cc. saline solution + 2.5 Gm. urea	1 plus
33	10.1	5	0.50	250 cc. saline solution + 2.5 Gm. urea	Absent

In studying the urine with sudan III a number of details must be observed. Failure to recognize them caused me to draw some erroneous conclusions, which were later corrected. A high concentration of the dye is necessary to stain the fat droplets. Between the time that the sudan III is placed in the urine or film and the time that the slide is examined at least five minute must elapse. Orange-stained droplets less than 3 to 4 microns in diameter are either contaminants or undissolved stain. Only fresh stain should be used.

In 7 of the experiments the urinary flow from the isolated kidney was sufficient, averaging from 15 to 25 cc. per hour. Fat droplets were present in the urine in numbers varying from 6 to 25 per low-powered field. Sections of all the kidneys showed an abundance of fat throughout the parenchyma. These experiments showed conclusively that intravascular fat was excreted through the kidneys,

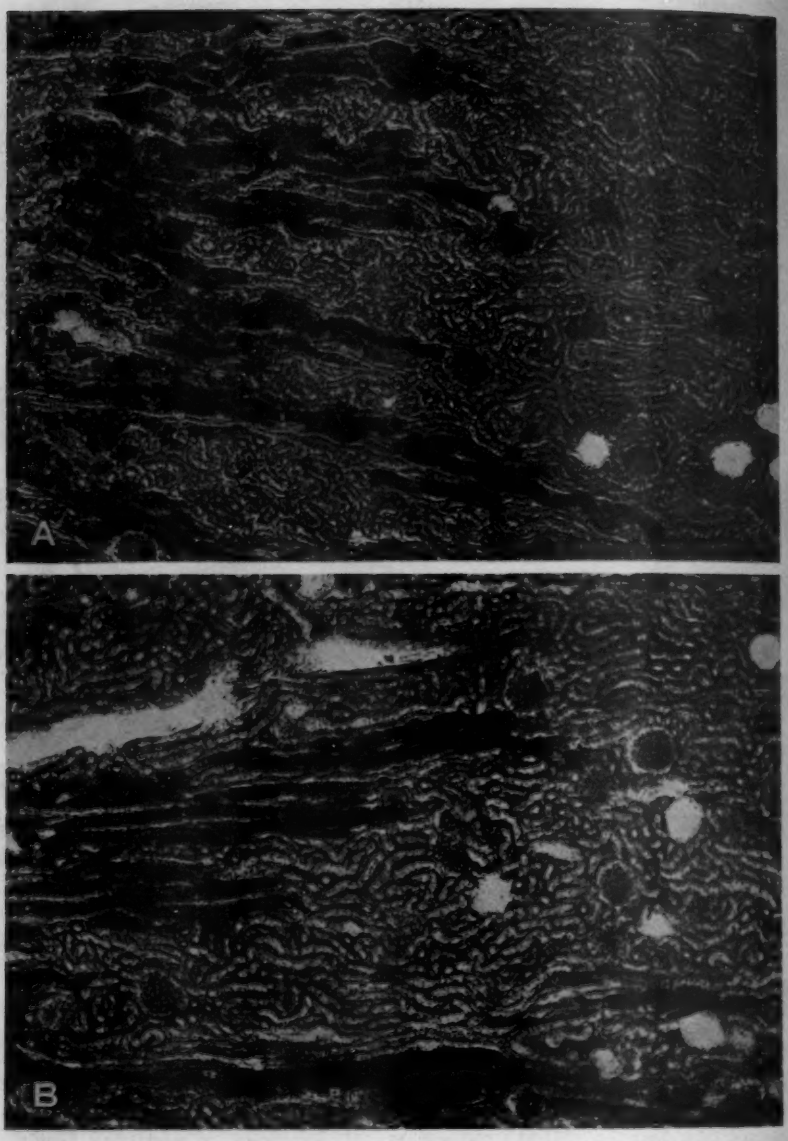

Fig. 1.—*A*, dog kidney stained with sudan III; × 33. Note the large amount of fat in the tubules. This animal received 3 cc. of dog marrow fat intravenously and was killed one hour later. *B*, dog kidney stained with sudan III; × 33. This animal received a dose of 0.012 cc. of olive oil intravenously. These few tubules show the selective absorption by the tubular cells. This animal was killed one hour after the injection.

at least under certain circumstances. A résumé of these experiments is presented in table 1.

In another series of experiments the fat was injected into a vein of the leg instead of into the renal artery. Decreasing doses of olive oil were given, and the urine was again collected from a cannulated ureter. It was found that when less than 0.75 cc. of olive oil was injected intravenously per kilogram of body weight the fat could no longer be detected in the urine. A résumé of these experiments is found in table 2.

Careful examination of the sections of the kidneys of these animals gave no clue as to just how the fat was excreted through the kidneys. The fat was found in the glomeruli in some and in the tubules alone in others. However, as a general rule, the droplets were found in both the glomeruli and the tubules in the same section. No fat was found in Bowman's capsule; however, it was present in the lumens of the tubules. There seemed to be no correlation between the amount of fat excreted and the location of the fat in the sections.

The experiments were then carried to the frog. In this animal the kidney has a dual blood supply. The glomeruli are supplied by the renal artery, while the tubules are supplied by the renal portal vein. In most frogs there is little overlapping of the circulation to the respective parts.

Large Louisiana bull frogs were used. Perfusion of the kidneys were done according to the method described by Cullis.[1] The perfusion solution throughout the experiments was amphibian Ringer-Locke solution with 0.4 per cent urea. The glomerular system was under 25 cm. of water pressure, while the tubules were kept at 10 cm. of water pressure, these pressures simulating those under which the normal amphibian kidney functions. Air was continually bubbled through both solutions so as to keep the oxygen content from becoming depleted. The right ventricle of the heart was opened so as to permit the perfusion solution to flow out, otherwise the overloaded circulation would stop. The urea was added to increase the urinary flow. Five-tenths cubic centimeter of emulsified olive oil was injected into the perfusing solution in each experiment, and the urine was collected in a test tube from the cannula inserted in the ureter.

Of the 18 experiments, in 10 there was sufficient urinary secretion for examination—3 when the fat was injected into the tubular system. These experiments suggested that the fat was excreted through the tubules only. For a résumé of these experiments see table 3.

In order to evaluate the consistency of these results, experiments were again made on dogs. MacNider[2] showed the value of destruction of the convoluted tubules of dogs by uranium for studies on urinary secretion. His technic was followed. If the assumption is correct that the fat given in the experiments described was excreted by the tubules, fat should no longer be excreted in the urine if the tubules were destroyed.

Dogs under 1 year of age were selected. Two milligrams of uranium nitrate per kilogram of body weight was injected into the buttocks. MacNider noted the maximum effect of the uranium in about nine days and the earliest return to normalcy in the surviving animals in nineteen to twenty-one days. For this reason each animal was given an injection of uranium and an interval of nine days was

1. Cullis, W. C.: J. Physiol. **34**:250, 1906.

2. MacNider, W. DeB.: Proc. Soc. Exper. Biol. & Med. **11**:159, 1914; J. Exper. Med. **26**:1, 1917.

TABLE 3.—*Experiments on Frogs*

Frog	Frogs' Perfusion Solution	Time, Min.	Urinary Secretion	Fat	Additional Drugs	Fatty Substance	Site of Injection	Location of Fat in Sections Stained with Sudan 3	Comment
3	Amphibian Ringer-Locke	90	1 plus	.....	Urea 0.4%	0.5 cc. emulsified olive oil	Aorta	Fat in glomeruli, some in vessels, none in tubules	
5	Amphibian Ringer-Locke	120	1 plus	1 plus	Urea 0.4%	0.5 cc. emulsified olive oil	Vein (renal portal)	Slides lost	Oil droplets present in urine
10	Amphibian Ringer-Locke	55	4 plus	4 plus	Urea 0.4%	0.5 cc. emulsified olive oil	Vein	Massive quantities in entire tubular system, none in glomeruli	
11	Amphibian Ringer-Locke	30	2 plus	?	Urea 0.4%	.....	Aorta	Fat in glomeruli and vessels, none in tubules	
12	Amphibian Ringer-Locke	40	1 plus	.....	Urea 0.4%	0.5 cc. emulsified olive oil	Vein	Oil in tubules, some droplets in glomeruli	Large amount of intratubular oil makes it certain there would have been fat in urine if experiment had run long enough
13	Amphibian Ringer-Locke	60	1 plus	1 plus	Urea 0.4%	0.5 cc. emulsified olive oil	Vein	Oil in tubules, none in glomeruli	
14	Amphibian Ringer-Locke	55	1 plus	4 plus	Urea 0.4%	0.5 cc. emulsified olive oil	Vein	Oil in tubules, none in glomeruli	
15	Amphibian Ringer-Locke	60	2 plus	2 plus	Urea 0.4%	0.5 cc. emulsified olive oil	Vein	Oil in tubules, none in glomeruli	
16	Amphibian Ringer-Locke	60	2 plus	2 plus	Urea 0.4%	0.5 cc. emulsified olive oil	Vein	Oil in tubules, none in glomeruli	
18	Amphibian Ringer-Locke	60	4 plus	2 questionable droplets	Urea 0.4%	0.5 cc. emulsified olive oil	Aorta	Oil in glomeruli	Many fat droplets present in tubules. Large quantity indicates overlapping of blood supply

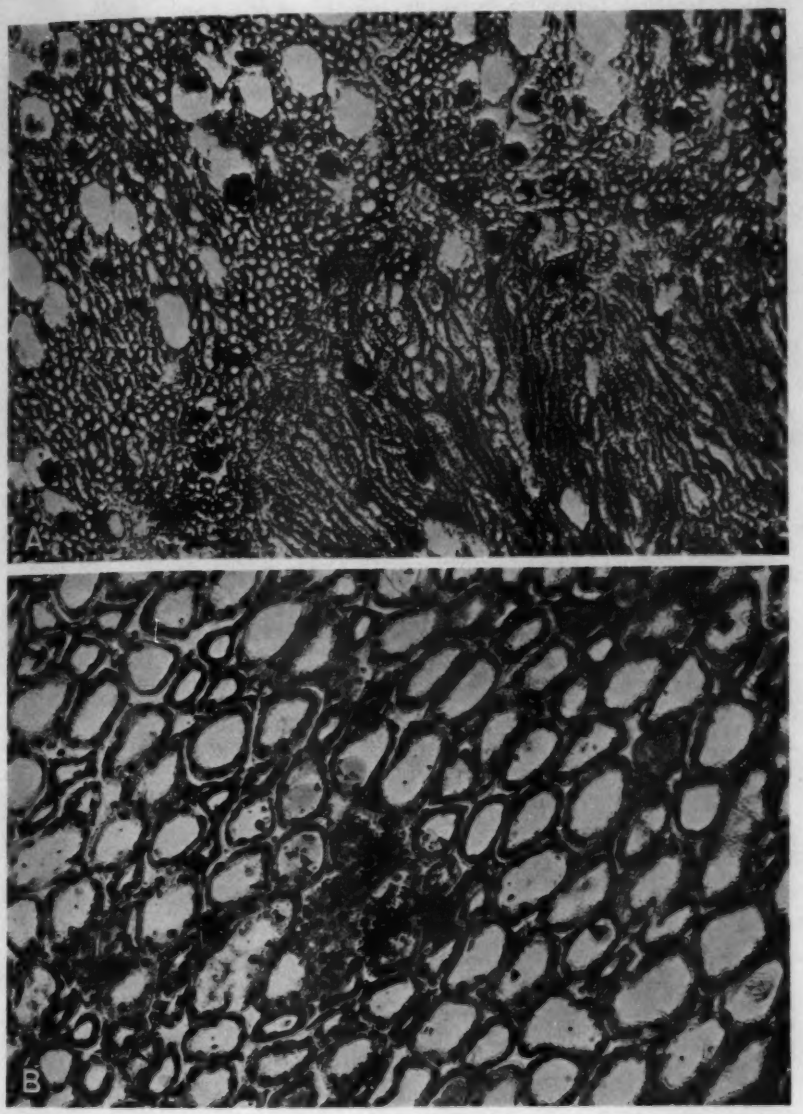

Fig. 2.—*A*, frog kidney stained with sudan III; × 34.5. This kidney was perfused with amphibian Ringer-Locke solution in both the glomerular and the tubular system. However, 0.5 cc. of olive oil injected into the renal artery reached only the glomeruli. No fat is visible in the tubules. The perfusion was permitted to run ninety minutes. *B*, frog kidney stained with sudan III; × 136.0. This kidney was perfused with amphibian Ringer-Locke solution in both the glomerular and the tubular system. However, 0.5 cc. of olive oil injected into the portal iliac vein reached only the tubules. The perfusion was permitted to run ninety minutes. No fat was visible in the glomeruli. Some of the fat is visible in the lumens of the tubules just to the left of the center of the field.

allowed to elapse before the intravascular injection of fat and collection of urine were carried out. In the first two experiments 2 mg. of uranium was injected per kilogram of body weight. In 1 animal all the tubules were not destroyed. In the remaining experiments 2.5 mg. was injected, which destroyed all the tubules without causing death of the animals. One cubic centimeter of olive oil was injected into the general circulation in each animal. The same technic was used in these experiments as in those represented in table 2.

Six experiments were made. In 4 of the animals there was complete suppression of fat excretion. One dog did not have all the tubules destroyed, as shown by section of the kidney. In this animal there was 2 plus fat excretion in the urine. The remaining animal showed 1 plus secretion of fat. For a résumé of these experiments see table 4. From these experiments it seems safe to say that excretion of fat occurs through the tubules only.

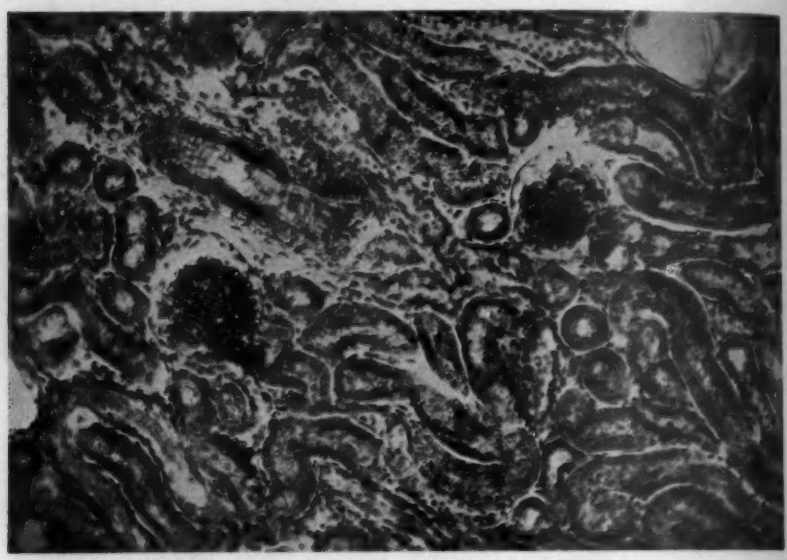

Fig. 3.—Dog kidney stained with sudan III; × 70.5. This animal had received 2.5 mg. of uranium nitrate per kilogram of body weight to destroy the convoluted tubules. Nine days later 1 cc. of olive oil was injected intravenously. Note the cloudy swelling and poorly stained cell markings of the destroyed tubules. No fat was picked up by these cells. Compare this section with figure 1 *A*.

It was desired to determine quantitatively how much of the intravascular fat was excreted in the urine. First 120 cc. of a normal dog's urine was divided into equal portions. To the first half 5 cc. of olive oil was added. This was thoroughly mixed with the urine by vigorous shaking. The mixture was placed in a separatory funnel and extracted with an equal volume of ether. The ether extract was separated from the urine and placed in a hot water bath; when the residue became small, the remaining portion was treated by a hot water bath at lowered pressure.

The oily residue was next centrifuged at high velocity for fifteen minutes and measured in a graduated centrifuge tube. Four and seven-tenths cubic centimeters of the original 5 cc. of olive oil was collected, showing a collectibility of 94 per cent by this method.

The second 60 cc. of normal dog's urine was extracted by the same method to determine whether or not there was present in the urine of normal dogs any fat extractable by ether. No fat was collected. As an additional control study, the urine of a dog on a starvation diet and the urine of one which had received a quart (about 1,000 cc.) of milk and cream were examined, with equally negative results.

Two dogs weighing 6.4 and 12.3 Kg. were given intravenously 1 cc. of olive oil per kilogram of body weight. They were placed in individual metabolism cages. A general diet was given, and their urine was collected and extracted at the end of twenty-four and forty-eight hours. From neither urine was any fat collected.

TABLE 4.—*Failure of Excretion of Fat Through Kidneys in Dogs Poisoned with Uranium*

Dog	Weight, Kg.	Uranium, Mg. per Kg.	Urinary Secretion	Oil in Urine*	Observations on Kidney Sections
1	5.9	2	4 plus	2 plus	Glomeruli normal, with no fat; convoluted tubules three fourths destroyed, fat present; Henle's loop, with moderate amount of fat
2	6.36	2	4 plus	0	Glomeruli normal, with no fat; convoluted tubules destroyed, with no fat; Henle's loop degenerative, with little fat
3	6.71	2.5	4 plus	0	Glomeruli normal, with no fat; convoluted tubules destroyed, with no fat; Henle's loop degenerative, with little fat
4	5.23	2.5	4 plus	1 plus	Glomeruli normal, with no fat; convoluted tubules destroyed, with no fat; Henle's loop degenerative, with little fat
5	3.75	2.5	2 plus	0	Glomeruli normal, with no fat; convoluted tubules destroyed, with no fat; Henle's loop degenerative, with little fat
6	4.55	2.5	4 plus	0	Glomeruli normal, with no fat; convoluted tubules destroyed, with no fat; Henle's loop degenerative, with little fat

* Nine days elapsed between the injection of uranium and the injection of olive oil. All animals received 250 cc. of physiologic solution of sodium chloride and 2.5 Gm. of urea during the period that the olive oil was being injected.

From these observations it seems safe to state that the amount of fat excreted in the urine is never sufficient to be of any quantitative significance.

SUMMARY

In experiments on animals, after intravenous injections of oil and bone marrow fat the fat was excreted through the kidneys provided that the quantity injected was not less than 0.75 cc. of olive oil per kilogram of body weight. This was detectable microscopically in the urine. Fat was never present in the urine in sufficient quantities to be demonstrated macroscopically. Fat appeared to be excreted through the tubules only, for uranium poisoning which destroyed the tubules prevented the excretion of intravascular fat.

ETIOLOGY OF HYPERTENSION RESULTING FROM COARCTATION OF THE AORTA

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In coarctation of the aorta of the adult type stenosis or atresia occurs at the isthmus, i. e., the portion of the aorta between the opening of the left subclavian artery and the origin of the ductus arteriosus. Abbott[1] attributed the stenosis to "congenital maldevelopment of the embryonic arterial wall at the junction of the primitive left 4th arch with the left 6th (ductus) so that the obliterative process going on in the latter takes effect also in the immediately contiguous tissue."

Blackford,[2] King,[3] Abbott[4] and Lewis[5] have given good descriptions of the developmental, clinical and pathologic features.

The characteristic clinical signs and symptoms are hypertension in the upper extremities with normal or low femoral blood pressure, reduced amplitude of the femoral pulse and peculiar notching of the inferior borders of the ribs, demonstrable in the roentgenogram. Anatomically there is marked stenosis of the isthmus of the aorta with extensive collateral circulation between the intercostal and the subclavian and internal mammary arteries.

The purposes of this paper are to give a description of coarctation of the aorta as observed in 5 adults who came to postmortem examination to describe experiments on dogs in which acute hypertension was produced by partial or complete occlusion of the aorta and to discuss the relation which this experimental hypertension bears to the hypertension found in adults with coarctation of the aorta.

CLINICAL CASES OF COARCTATION OF THE AORTA IN ADULTS

Since 1910 coarctation of the aorta in an adult has been noted in only 5 of approximately 35,000 autopsies performed by the department of pathology at the University of Minnesota.

From the Department of Pathology, University of Minnesota, Minneapolis.

1. (*a*) Hamilton, W. F., and Abbott, M. E.: Am. Heart J. **3**:381, 1928. (*b*) Abbott, M. E.: ibid. **3**:392, 1928.

2. Blackford, L. M.: Arch. Int. Med. **41**:702, 1928.

3. King, J. T., Jr.: Arch. Int. Med. **38**:69, 1926.

4. (*a*) Abbott, M. E.: Am. Heart J. **3**:574, 1928. (*b*) Hamilton and Abbott.[1a] (*c*) Abbott.[1b]

5. Lewis, T.: Heart **16**:205, 1931.

CASE 1.—A white man 21 years of age had been apparently well until shortly before death. He made no complaint when he went to bed at 10 p. m., but about 4 a. m. his parents found him gasping for breath. He died before medical assistance could be obtained.

Autopsy.—The tissues of the mediastinum were infiltrated with blood. The pericardium was markedly distended with fresh blood. The heart was contracted and firm, the epicardium smooth and glistening. The left ventricle showed definite hypertrophy; the right ventricle was normal. About 1 cm. above the anterior sinus of Valsalva there was a flattened V-shaped rupture of the aorta, the total length of which was 2.5 cm. There was a dissecting aneurysm of the ascending aorta which involved about one half of its circumference and which had ruptured into the pericardium as well as into the mediastinum. Just below the level of the ductus arteriosus there was a marked constriction of the aorta. The lumen was reduced to about one-third the normal diameter. The ductus arteriosus was closed. The lumen of the aorta proximal to the stricture was markedly dilated, especially at the root of the aorta. The walls, however, showed no apparent thinning. No other abnormalities of the aorta were seen.

The right kidney weighed 20 Gm. There was moderate dilatation of its pelvis, and the cortex was very thin. There was complete closure of the lumen of the ureter at the ureteropelvic junction. Elsewhere the ureter was patent. The left kidney weighed 305 Gm. and appeared normal. There were no lesions in the brain or other organs.

Summary.—Coarctation of the aorta, hypertrophy of the left chambers of the heart and rupture of the arch of the aorta.

CASE 2.—A white man 23 years of age noticed, in January 1930, that his abdomen was enlarging. His health had been good, and he had done all the regular work of a farmer.

On admission, March 6, 1930, the blood pressure in the arm was 165 systolic and 95 diastolic; the pulse rate, 76 per minute and irregular. The inferior margin of the liver was about 4 cm. below the costal margin in the right midclavicular line. The fluid removed from the abdominal cavity showed 0.4 per cent albumin and a specific gravity of 1.019. The icterus index was 12 and the van den Bergh reaction was indirect. The Wassermann reaction was negative. Roentgen study showed massive cardiac enlargement to both right and left. Notching of the inferior borders of the ribs indicated enlarged intercostal arteries. A diagnosis of coarctation of the aorta was made. The esophagus was displaced by the large left auricle. An electrocardiogram showed bradycardia and left bundle branch block. A Talma-Morison operation was performed, since it was felt that the patient had two lesions: cirrhosis of the liver and coarctation of the aorta. He obtained some relief and was discharged.

About October 25 he experienced sudden dizziness, weakness, palpitation and moderate precordial pain. He lay down for seven to eight minutes, gasping for breath. Two days later he had a similar attack lasting five minutes.

Examination at this time showed slight cyanosis and marked pulsation of the vessels of the neck. Markedly dilated veins were visible over the chest. Pulsations of intercostal arteries were palpable over the back and right side. The heart tones were loud and irregular. The blood pressure in the left arm was 134 systolic and 104 diastolic, and that in the right arm was 130 systolic and 104 diastolic. The liver was palpable 12 cm. below the xiphoid process and easily ballotable. The abdominal veins were prominent. Marked tortuosity of

the vessels of the ocular fundi was seen (none was noticeable in the smaller ones), but no hemorrhages or exudates were found. The patient was cyanotic and weak almost continuously after his admission. At 5:40 p. m. November 7 his hands were extremely cold, and he was perspiring profusely. In a few minutes he began to gasp and died.

Autopsy.—The heart measured 20 cm. in its transverse diameter; the transthoracic diameter of the chest was 27 cm. The heart was not weighed. There was no disease of the valves, and no defects of the septums were seen. The ascending aorta was normal. The left common carotid artery was moderately dilated. The left subclavian artery was so dilated that it equaled the innominate artery in size. Marked constriction of the aorta was present at the isthmus. At this point the lumen of the aorta was so narrowed that only a very small probe could be passed through. Distal to the constriction the aorta was small. The intercostal and internal mammary arteries were markedly dilated, the first left intercostal being as large as the left carotid artery. The head and neck were not examined. The liver showed marked chronic passive congestion, but there was no evidence of cirrhosis.

Summary.—Coarctation of the aorta, hypertrophy of the left ventricle and congestive heart failure.

Case 3.—A white man 33 years of age was admitted to the hospital Oct. 1, 1935. Two months previously he had fainted on the street. He had had some dyspnea since childhood, and had been told some years before that he had high blood pressure. September 23 he suffered from chills, fever, a nonproductive cough and anorexia. He became weak and dizzy and had a severe ringing in his head. For six days he had watery diarrhea, but the feces showed no blood, mucus or pus. The blood pressure was 160 systolic and 70 diastolic. The heart was enlarged and boat shaped, although roentgen study seven weeks previously had shown a normal-sized heart. Systolic and diastolic apical murmurs were heard, the diastolic louder at the left sternal border. Definite pulsations and a systolic murmur were found over the fourth, fifth and sixth intercostal arteries on the left and over the third on the right. The Wassermann reaction was negative. An electrocardiogram showed low voltage and prolonged PR intervals. Roentgen study showed erosion of the inferior margins of most of the ribs. The conclusion was that the patient had coarctation of the aorta with left ventricular enlargement. The temperature was 103 F. on admission and rose to this height daily. The hemoglobin content was 67 per cent. The red cell count was 3,800,000. The leukocyte count was 13,800, with 80 per cent polymorphonuclears. The patient became weaker and died October 16.

Autopsy.—The examination was limited to the chest. The internal mammary arteries were four times the normal diameter, with walls proportionally thickened. The right and left pleural cavities contained, respectively, 1.5 and 1 liter of clear amber fluid. The pericardial sac contained 100 cc. of sanguineous fluid. The heart weighed 560 Gm. with the arch of the aorta attached. The epicardium was covered with a thin, shaggy fibrinous exudate. The left ventricular wall was thickened. The pulmonary, tricuspid and mitral valves were normal. The aortic valve was bicuspid. Its leaflets were greatly distorted by old and recent inflammatory changes and were adherent at the commissures, where there was thickening by old calcified scar tissue. Large fresh vegetations were present on all the leaflets of the aortic valve, and one of the cusps was ulcerated at its base. At the base of the left ventricle was an ulcer filled with a thrombus 1 cm. in width. The coronary arteries were unusually large but showed no atherosclerosis.

A slight atheromatous change was present at the aortic ring, but the remainder of the aorta was smooth. The inner circumference of the aorta at its origin measured 7.5 cm. Five millimeters above the aortic ring the vessel was 8 cm. in diameter. Just distal to the origin of the left subclavian artery a projecting shelf surrounded the lumen of the aorta like a diaphragm. The diaphragm was about 4 mm. in breadth, with a 1 mm. opening at its center. Immediately proximal to the diaphragm was a conical outpouching of the aorta from its inner curvature. At the apex of this pouch a tiny capillary lumen communicated with the pulmonary artery at its bifurcation (vestige of the ductus arteriosus).

Summary.—Coarctation of the aorta, bicuspid aortic valve and bacterial endocarditis.

CASE 4.—A man 22 years of age had a severe attack of scarlet fever in 1924, which was followed by symptoms and signs of nephritis and hypertension. The systolic blood pressure at that time ranged from 200 to 280 mm. of mercury, and moderate to severe albuminuria was present. About 1930 he was hospitalized for seven months, with symptoms of congestive heart failure. His life was fairly normal, and he held various jobs involving mild physical labor. About midnight of Oct. 14, 1938, he experienced a severe pain in the back of his neck associated with very severe headache. He was hospitalized at once. On admission the systolic blood pressure exceeded 300 mm. of mercury and the diastolic was 150. Respirations were of the Cheyne-Stokes type, and the patient vomited repeatedly. He succumbed four hours after the onset of the attack.

Autopsy.—The heart weighed 1,120 Gm. The left ventricle showed great hypertrophy, mainly of the concentric type, with some dilatation. The right ventricle showed marked dilatation and hypertrophy but was considerably overshadowed by the left. The auricles were dilated. The valves were not diseased, the aortic valve having three normal cusps. Midway between the mitral valve and the apex the wall of the left ventricle was 3.7 cm. thick. The root of the aorta showed moderate dilatation. The coronary arteries were of large caliber. Distal to the point where the left subclavian artery arose, the aorta was constricted, measuring 1 cm. in its outside diameter. Beyond this point the aorta appeared abnormally small, its diameter at the level of the fourth lumbar vertebra being 1 cm. The diameter of the innominate artery at its origin was 1.7 cm. Proximal to the constriction there was a saccular outpouching of the aortic wall with a constricted neck. Its capacity was about 15 cc., and its wall was almost completely calcified. The rest of the aorta showed little or no atheromatous change. No notching of the ribs could be palpated. The internal mammary arteries were enlarged, their inner diameter measuring 5 to 6 mm. Many vessels were seen coursing through the rectus muscles. The head was not examined. The liver, lungs, kidneys and spleen all showed evidence of severe acute congestive heart failure. There were no changes in the kidneys suggestive grossly or microscopically of either primary hypertension or chronic glomerulonephritis.

The head was not examined post mortem, but it appears probable from the clinical evidence that death was due to intracranial hemorrhage.

CASE 5.—A white man 21 years of age was quite well until March 1936, when he began to have pain in the shoulders and feet and later in the left hand. Pain and loss of motion were present, but there was no heat, redness or swelling. After two weeks in bed he still had fever, and his heart rate was 120. His physician diagnosed heart disease. In July 1936 his tonsils were removed, and there was considerable postoperative bleeding.

He was first seen at the University Hospital in July 1937. At that time his complaints were palpitation, dyspnea (increased with activity) and a loss of 20 pounds (9.1 Kg.) in weight during the last eighteen months. The blood pressure was 186 systolic and 68 diastolic (220 systolic and 70 diastolic on one occasion); the pulse rate, 90; the respiratory rate, 20. There was shortness of breath on slight exertion. The ocular fundi showed no definite changes; the thyroid was palpable but not nodular. The heart was markedly enlarged to the right and the left (transverse diameter, 20.5 cm.; transthoracic diameter, 28.3 cm.). A definite capillary pulse was present in the fingers. Systolic and diastolic murmurs were heard in the left anterior axillary line. Fluoroscopic examination revealed the esophagus displaced to the right. The vital capacity was 3,200 cc. The electrocardiogram showed a PR interval of 0.26, notching of QRS, negative T_2 and T_3, and split P_1. The urine showed specific gravity of 1.017 and albumin (1+). The hemoglobin content was 100 per cent. At this time it was believed that he had aortic regurgitation and mitral regurgitation and stenosis all on the basis of an old rheumatic infection. About the middle of August 1938 dyspnea, orthopnea and edema were first present at rest. September 8 clear yellow ascitic fluid to the amount of 500 cc. was removed, and weakness and night sweats were observed. The patient was admitted to the hospital. Pulsations of the vessels of the neck were noted, and the veins were markedly distended. A diastolic murmur was heard over the aortic area and a systolic murmur at the apex. The blood pressure was 180 systolic and 80 diastolic; the pulse was regular. Rales were heard at the bases of the lungs. The liver was 3 cm. below the rib margin. There were ascites and severe edema of the lower extremities. A capillary pulse and a water hammer pulse were found in the upper extremity, but no Duroziez sign was present in the femoral pulse. After he had been on a cardiac regimen for a few weeks with some improvement, the blood pressure of the right arm was 208 systolic and 84 diastolic; that of the left arm, 196 systolic and 84 diastolic, and no pulsation or blood pressure could be obtained in the lower extremities. The urine showed specific gravity of 1.013 to 1.020 and albumin (a trace to 1+). The icterus index was 28, with a prompt direct van den Bergh reaction. The sedimentation rate was 13 mm. the first hour and 39 mm. the second hour. The Wassermann reaction of the blood was negative. The electrocardiogram revealed right axis deviation, a PR interval of 0.28 and a prolonged QRS interval. T_2 and T_3 were negative. In the roentgenogram the heart showed massive enlargement to the right and left. The left ventricle seemed greatly enlarged and the right atrium distended. Erosion and scalloping of the inferior surfaces of the posterior portions of the ribs were present. The clinical impression was coarctation of the aorta with heart failure. The course was downhill. Infarcts of the lungs developed terminally.

Autopsy.—The heart weighed approximately 900 Gm. The right auricle was dilated, and the right auricle and ventricle were markedly hypertrophied. The left auricle was moderately dilated and hypertrophied. Thickening of the wall of the left ventricle was extreme, the myocardium appearing normal. There was no disease of the valves, but the aortic valve was bicuspid. One cusp appeared normal; the other showed a median raphe. From the sinus of Valsalva on either side of the raphe arose the right and left coronary arteries. There was no evidence of atheromatous change in the aortic arch. Just distal to the origin of the left subclavian artery a thick fibrous remnant of the ductus arteriosus was seen; its diameter was 1 cm. and its length 1.5 cm. It connected the aorta to the pulmonary artery. On the inner surface of the pulmonary artery a dimpling was seen at the

point corresponding to the attachment of the ductus, but it ended blindly. Distal to the attachment of this fibrous remnant of the ductus, the aorta was markedly narrowed for a distance of about 1 cm., beyond which it widened again somewhat. Throughout the rest of its course it was small, its midabdominal circumference measuring 27 mm. The lungs showed thromboses of many branches of the pulmonary arteries with corresponding areas of infarction. The intercostal arteries, particularly the second, third and fourth, were dilated, in several instances to an internal diameter of 5 to 6 mm. The kidneys were normal grossly and microscopically. In this case the history and findings were confused with rheumatic aortic regurgitation and mitral stenosis and regurgitation.

Summary.—Coarctation of the aorta, bicuspid aortic valve and congestive heart failure.

Cases 2, 3 and 5 were diagnosed clinically.

ANALYSIS OF OBSERVATIONS IN CASES PREVIOUSLY RECORDED IN THE LITERATURE

Hamilton and Abbott [1a] stated that coarctation of the aorta of the adult type usually causes symptoms between the ages of 20 and 40 years. In the majority of patients the condition remains latent until early adult life, the gradual development of the collateral circulation keeping pace with the demands of the body until some intercurrent infection weakens the myocardium or some excessive muscular exertion brings on myocardial decompensation. From the point of view of symptomatology one may distinguish three types of the disease.

1. The condition is apparently latent throughout life. Either the lesion is an accidental observation at autopsy or it is the cause of sudden death through rupture of the aorta or through intracranial hemorrhage.

2. Cardiac insufficiency may suddenly develop from an apparently inadequate cause in a previously normal young adult and pass gradually or rapidly into complete cardiac decompensation followed by death.

3. Signs of vascular disease in the upper part of the body, with dyspnea and palpitation as evidences of cardiac fatigue, may exist from early childhood. The condition may terminate with cardiac failure, rupture of the aorta or intracranial hemorrhage.

Abbott [4a, c] has reviewed published reports of 200 instances of stenosis or obliteration of the descending arch, including observations at autopsy.

Anatomic Features.—In 47 cases in Abbott's series there was complete atresia; in 108 cases, extreme stenosis, and in 45 cases, a moderate degree of stenosis. In 46 cases the aortic valve was bicuspid.

In any case of extreme stenosis the aorta proximal to the constriction is greatly dilated, presumably as a result of the increased intravascular tension. The left ventricle is nearly always hypertrophied and is often dilated.

Anastomoses develop between the arteries above and those below the point of constriction. The major part of the new circulation is usually between the superior intercostal artery from the subclavian artery and the first aortic intercostal artery, which arises from the aorta just below the constriction, and also the posterior scapular, intrascapular and subscapular arteries, which conduct blood from the subclavian arteries into the second and sometimes into the fourth aortic intercostal artery, and thence into the aorta below the constriction. The intercostal arteries become very large, and they usually erode the lower borders of the ribs. The aorta immediately below the constriction, where the upper three aortic intercostal arteries are given off, is frequently dilated in a bulbous fashion and may resemble an aneurysm. It resumes its normal or a diminished caliber at the level of the fourth or the fifth intercostal artery, which usually take no part in the anastomosis but supply their own district from the blood which reaches them through the aorta.

It is of interest to remember that the circulation for the lower part of the body is derived practically entirely from the subclavian arteries, which assume a great size, while the carotid arteries are usually relatively little changed.

A diminished femoral pulse or even absence of this pulse is pathognomonic of coarctation, especially when there are dilated, pulsating vessels or arterial murmurs in the interscapular and other regions of the thoracic wall. The diminution of the femoral pulse, however, is not constant and does not seem related to the degree of stenosis of the aorta. The fact that the lower extremities are well supplied with blood when the femoral pulse is greatly diminished is not easy to understand. The diminution of the femoral pulse is not due to the reduction in the volume of blood passing through the constriction in the aorta but to the fact that the blood passes through numerous collaterals and does not reach the lower aorta simultaneously. It therefore causes a more gradual rise of the pulse wave and a more rounded upper curve. As a result, the palpating finger obtains the sensation of a delayed, weak pulse. The force of the pulse is thus determined not by the degree of stenosis but by the directness of the path of the blood back to the aorta.

There is a marked difference in systolic blood pressure between the upper and the lower extremities, but the diastolic pressure is about the same.

Overtaxing of the circulation in the upper part of the body may be revealed by a sense of fulness in the head, buzzing of the ears, violent pulsation in the neck, flushing and lividity of the face, stabbing pains in the back, shoulders and extremities and over the precordium, epistaxis, hemoptysis and periods of severe headache.

Sex.—In the group with coarctation of the aorta reported by Abbott [48] there were 147 males and 48 females.

Age at Death.—The highest mortality was in patients in the second, third and fourth decades of life, the numbers dying being, respectively, 45, 49 and 45, or 139 of the 200 patients (Abbott).

Causes of Death.—In 155 of the 200 patients studied by Abbott (i. e., 77 per cent) the coarctation or a complicating cardiac lesion was the cause of death. Spontaneous rupture of the heart or of the aorta took place in 40, while in 4 others rupture of a mycotic aneurysm of the aorta occurred, making a total of 44 who died from rupture of the heart or aorta (22 per cent). In 10 other patients there was mycotic endarteritis in the descending arch at or just below the coarctation, the condition in these patients running the course of a subacute bacterial infection. Twenty-four others died from the effects of cerebral lesions, usually hemorrhage. Sixty patients died from failing compensation, and 17 died suddenly from cardiac asystole or without apparent cause.

EXPERIMENTAL ACUTE HYPERTENSION FROM OBSTRUCTION OF THE AORTA

Goldblatt [6] and others have found in chronic experiments that by stenosing the renal arteries and thereby decreasing the blood supply to the kidneys a persistent elevation of blood pressure can be obtained. It was first demonstrated [7] that decreases in the lumen of the main renal artery by varying degrees of compression cause immediate corresponding decreases of blood flow through the kidney. A decrease of intraglomerular capillary pressure as a result of this procedure has been assumed by Goldblatt but not proved.[6] In a series of experiments, by the use of this method it has been found that in the dog [8] and the monkey [9] constriction of the main artery of one kidney results in an elevation of blood pressure which persists for weeks or months but usually returns to a lower or to the original level within one month. Adequate constriction of both main renal arteries at the same time or with an interval between the clampings results in persistent hypertension. The same persistent effect on the blood pressure has been obtained by first constricting the main artery of one kidney and later removing the other kidney. In some animals with both renal arteries constricted

6. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia, in Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938, p. 237.

7. Goldblatt, H.; Lynch, J.; Hanzal, R., and Summerville, W.: J. Exper. Med. **59**:347, 1934.

8. (*a*) Goldblatt, H.: Tr. & Studies, Coll. Physicians, Philadelphia **6**:5, 1938. (*b*) Goldblatt, H.; Lynch, J.; Hanzal, R., and Summerville, W. W.: Bull. Acad. Med. Cleveland **16**:6, 1932. (*c*) Goldblatt, H.: Ann. Int. Med. **11**:69, 1937.

9. Goldblatt, H.: J. Exper. Med. **65**:671, 1937.

the elevated blood pressure tends after a while to return to a lower level. This is probably due to the development of a significant accessory circulation to the kidney, which is naturally abundant in the dog. In such dogs increasing the constriction of the main renal arteries usually results in reelevation of the blood pressure.

The mechanism of development of the benign phase of experimental hypertension induced by renal ischemia has been assumed, for the same reasons as in the case of human essential hypertension,[10] to be an increase in peripheral resistance. Since in the experimental animals this cannot be regarded as due to initial organic change in the peripheral portion of the entire vascular system, the problem narrows down to the cause of the functional increase of peripheral resistance which follows constriction of the main renal arteries. There are but two known mechanisms whereby generalized constriction of arterioles[10a] and increased peripheral resistance can be produced, namely, either a nervous reflex from the ischemic kidneys, which affects the general vasomotor apparatus, or a humoral mechanism initiated by the ischemic kidneys and due to formation or accumulation in the blood of a substance which directly or indirectly constricts the peripheral vessels.

If the main renal artery of one kidney is constricted, and the ischemic kidney is removed sometime later, when the blood pressure is still well elevated, the blood pressure falls promptly to the normal level.[8c] If, instead of nephrectomy, the clamp on the one ischemic kidney is released or removed, the blood pressure returns promptly to the original level.[8c] If in a hypertensive animal both clamps are released, the blood pressure falls promptly to the original normal level.[8c] Bilateral nephrectomy is not followed by the development of persistent hypertension.[11] These results constitute evidence that the kidney is responsible for the effect and that it must be present in the body in order for hypertension to occur.

In dogs denervation of the renal pedicle [12] does not prevent or reduce hypertension due to constriction of the main renal arteries. Nor does section of the splanchnic nerves with excision of the lower four thoracic sympathetic ganglions,[13] section of the anterior nerve roots from the sixth dorsal to the second lumbar inclusive,[14] or excision of the entire sympathetic nervous system in the thorax and abdomen, including

10. (*a*) Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934. (*b*) Prinzmetal, M., and Wilson, C.: J. Clin. Investigation **15**:63, 1936.

11. Cash, J. R.: Proc. Soc. Exper. Biol. & Med. **23**:609, 1926. Goldblatt.[8c]

12. Collins, D. A.: Am. J. Physiol. **116**:616, 1936.

13. Goldblatt, H.; Gross, J., and Hanzal, R.: J. Exper. Med. **65**:233, 1937.

14. Goldblatt, H., and Wartman, W. B.: J. Exper. Med. **66**:527, 1937.

cardiac denervation [15] and even pithing,[16] prevent or permanently reduce hypertension produced by constriction of the main renal arteries. Finally, when one kidney is removed and the other kidney is transplanted to the neck or to the inguinal region and its main renal artery constricted, the blood pressure rises.[17] In such an animal there is no possible direct connection between the kidneys and the nervous system. The results of these studies eliminate a nervous reflex from the ischemic kidneys as the mechanism responsible for the initiation of the hypertension and leave only a humoral mechanism as the probable explanation of the phenomenon.

Goldblatt [18] found also that stenosis of the aorta above the origin of both renal arteries resulted in persistent elevation of blood pressure while stenosis below the origin of these vessels did not cause hypertension.

Rytand,[19] using increase in the weight of the heart in the rat as evidence of hypertension, obtained similar results. Stenosis of the aorta below the right but above the left renal artery, he found, also produced hypertension; however, if the distal kidney (left) was removed, hypertension did not result.

Goldblatt's [8a] conclusion was that hypertension from experimental aortic stenosis is of the same nature as that due to stenosis of the renal arteries directly, i. e., that stenosis of the aorta causes elevation of blood pressure by producing renal ischemia.

This idea was further expanded by Rytand [19a] and Goldblatt [20] to the supposition that renal ischemia with the "pressor substance" resulting from it is the important factor in the elevation of blood pressure so regularly found in the upper extremities in coarctation of the aorta.

In 1886 de Jager [21] showed that complete occlusion of the thoracic aorta caused increase in arterial blood pressure.

Barcroft [22] and Barcroft and Formijne [23] found that in dogs an average initial arterial blood pressure of 112 mm. of mercury was raised to 250 mm. by complete occlusion of the thoracic aorta. The output of the left ventricle was found to be increased 18 per cent by

15. Freeman, N. E., and Page, I. H.: Surgery **2**:487, 1937. Albert, L. K.; Alving, A. S., and Grimson, K. S.: Proc. Soc. Exper. Biol. & Med. **37**:1, 1937.

16. Glenn, F.; Child, C. G., and Heuer, G. J.: Ann. Surg. **106**:848, 1937.

17. Blalock, A., and Levy, S.: Ann. Surg. **106**:826, 1937. Glenn and others.[16]

18. Goldblatt, H., and Kahn, J. R.: J. A. M. A. **110**:686, 1938.

19. Rytand, D. A.: (*a*) J. Clin. Investigation **17**:391, 1938; (*b*) Proc. Soc. Exper. Biol. & Med. **38**:10, 1938.

20. Goldblatt, H., in discussion at a meeting of the American Association of Pathologists and Bacteriologists, Richmond, Va., April 7, 1939.

21. de Jager, S.: J. Physiol. **7**:130, 1886.

22. Barcroft, H.: J. Physiol. **71**:280, 1931; **72**:186, 1931; **78**:186, 1933.

23. Barcroft, H., and Formijne, P.: J. Physiol. **82**:377, 1934.

this procedure. In association with this, the right auricular pressure was found to rise. This indicates that the increase in systemic flow is to be attributed to an increase in inflow from the lower part of the body.

A similar occlusion of the thoracic aorta occurs in man in coarctation of the aorta. Although Goldblatt [20] and Rytand [19a] have expressed the opinion that the hypertension in patients with coarctation of the aorta is due to a pressor substance formed as a result of ischemia of the kidneys, there is much evidence that hypertension in such patients is of a mechanical nature. The experiments to be described were performed in an attempt to clarify the origin of this form of hypertension.

Levy and Blalock [24] gave the following values for blood flow to the various parts of the body concerned in the experiments (fig. 1 and table 1).

TABLE 1.—*Values for Blood Flow to Different Regions of the Body, According to Levy and Blalock* [24]

Region of Body	Percentage of Flow
A. Liver and portal bed	28.4
B. Kidneys (both)	18.5
C. Lower part of trunk and lower extremities	13.0
D. Head, upper part of trunk and upper extremities	31.3

Dogs were used, anesthetized with pentobarbital sodium, intraperitoneally injected. The carotid blood pressure was recorded, with the use of a cannula and the kymograph.

A screw clamp was placed about the aorta just above the origin of the celiac axis, 2 or 3 cm. above the origin of the right (upper) renal artery (fig. 1). The clamp was first closed partially and then completely. Immediately after partial narrowing of the aorta the pressure began to rise and reached its maximum within several heartbeats. Further stenosis raised the pressure still more, the highest values being found with complete closure of the aorta (fig. 2 *A*). This rise was maintained until the clamp was released. On release of the clamp there was an immediate drop in pressure, following which it gradually rose to about the original level. Moreover, partial release of the clamp caused a sudden but partial drop, and the pressure readings could be decreased in steps by releasing the clamp a little at a time (fig. 2 *B*).

After ligature of both renal pedicles no change in blood pressure was observed. Bridgman and Hirose [25] found no change in blood pressure with acute stenosis or occlusion of the renal arteries. In an earlier communication I [26] reported ligation only of the renal arteries. It was thought advisable in further experiments to clamp or ligate not only the renal arteries but also the rest of the renal pedicles to avoid the possibility of accessory circulation supplying the kidneys and substances thus formed leaving by way of the renal veins.

With the renal pedicles ligated, the aorta was again stenosed as described. Exactly the same type of rise and fall of blood pressure occurred. In one experi-

24. Levy, S. E., and Blalock, A.: Am. J. Physiol. **118**:368, 1937.
25. Bridgman, A. W., and Hirose, K.: Arch. Int. Med. **21**:351, 1918.
26. Brotchner, R. J.: Proc. Soc. Exper. Biol. & Med. **40**:264, 1939.

ment the rise in pressure was 76 mm. of mercury. This was maintained for over forty minutes. On release of the clamp the same type of sudden drop occurred. The average rise in 19 experiments was 58 mm. of mercury.

Section of both vagus nerves in one experiment did not prevent a marked rise in pressure when the aorta was subsequently clamped above the celiac artery.

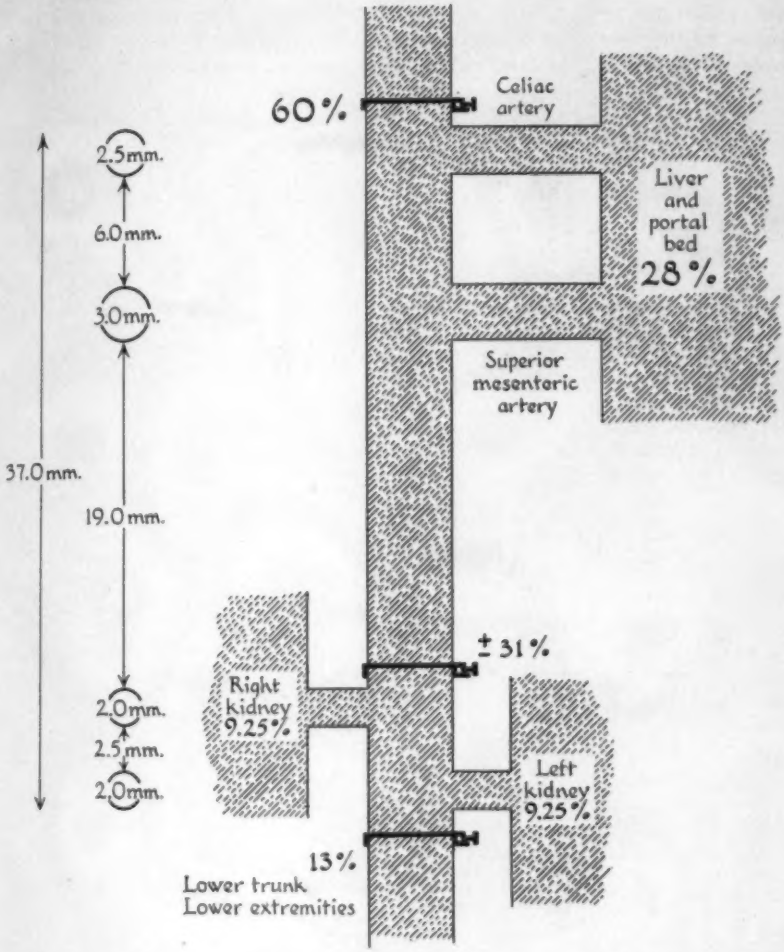

Fig. 1.—The levels of obstruction of the aorta and the amount of blood flowing to the various areas expressed in percentage of the output of the left ventricle (Levy and Blalock [24]). The values at the left are the average measurements of the vessels concerned and their levels of origin.

Barcroft [27] sectioned the vagus nerves as a routine before occluding the thoracic aorta and found a regular rise in blood pressure.

In one experiment the diaphragm was perforated with resultant pneumothorax. The pressure rose slowly to 204 mm. of mercury. When the aorta was clamped

27. Barcroft.[22] Barcroft and Formijne.[28]

above the celiac axis, a rapid rise to 274 mm. occurred, and on release of the clamp the pressure fell at once to 150 mm., the dog dying shortly afterward.

In another experiment the common carotid artery (the one opposite that cannulated for recording the pressures) was clamped for a few minutes and released. In three experiments the rise in pressure averaged 11 mm. of mercury. This clamping would obstruct a considerable amount of flow to the head, since no blood reached the head through the cannulated vessel. The rise could well be explained by the obstruction of flow, but one cannot deny that there may have been a carotid sinus reflex. The heart rate, however, seemed unchanged.

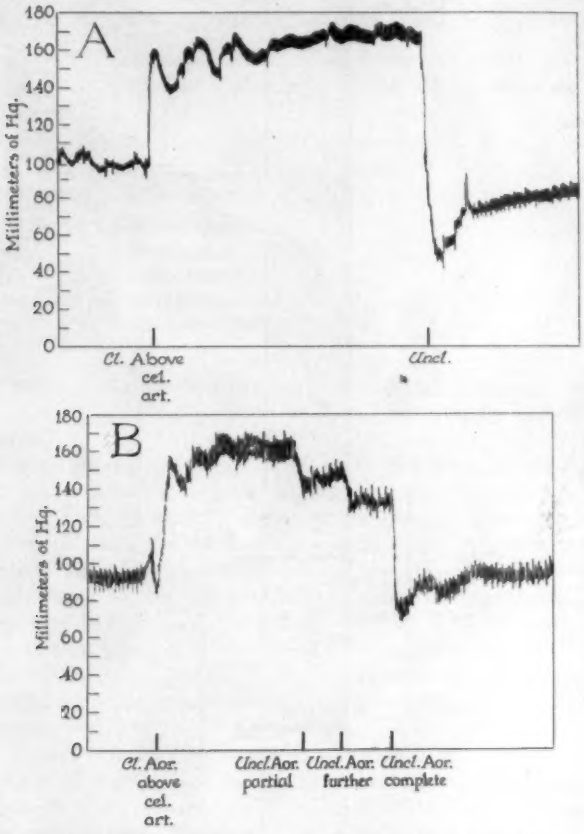

Fig. 2.—*A*, complete clamping of the aorta just above the origin of the celiac axis, and subsequent unclamping. *B*, complete clamping of the aorta above the celiac artery. The clamp was released a little at a time.

In four experiments with the pressure elevated by the clamp above the celiac axis, clamping of the carotid gave an increase, the rise averaging 14 mm., with a drop to the original high level on release.

In another experiment (fig. 3) the common carotid artery was clamped. A small rise (8 mm. of mercury) occurred at once. Next the aorta was clamped

above the celiac artery. The pressure rose rapidly to 180 mm. After a few minutes the clamp on the carotid artery was released. An immediate drop to a new level at 154 mm. occurred. After a few minutes the carotid was clamped again, and the pressure rose to the level previously maintained. It was released,

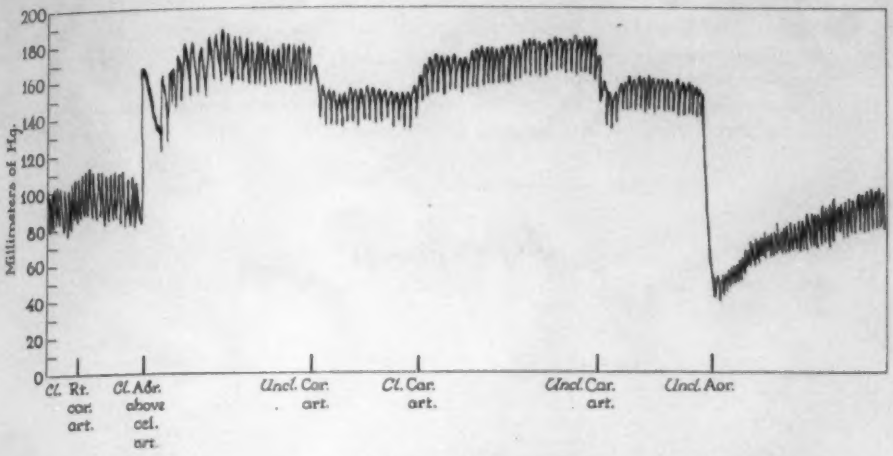

Fig. 3.—Right common carotid artery clamped, then aorta clamped above celiac artery. Carotid clamp released and then reclamped a little later. Carotid clamp released, and clamp on aorta released.

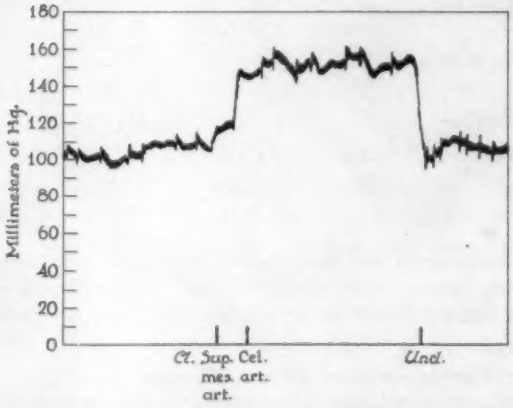

Fig. 4.—Superior mesenteric artery and celiac axis clamped, then unclamped.

and then the aorta was unclamped, the pressure returning to normal levels. These changes indicate a mechanical rather than a reflex change.

In another experiment in which clamping of the aorta above the celiac artery gave rises averaging 78 mm. of mercury in two trials, the celiac and superior mesenteric arteries were clamped (fig. 4). A rapid rise (average, 59 mm. in two

trials) occurred, and following release of the clamps a rapid fall to normal levels took place. Longcope and McClintock [28] had a similar experience.

The aorta was clamped completely above the origin of the celiac artery. The pressure rose to 156 mm. of mercury. The clamp was released, and the pressure returned at once to normal. Next the celiac, superior mesenteric and renal arteries were clamped, and following this the aorta was closed *below* the origin of the renal arteries (fig. 1). The pressure rose to 152 mm., since approximately the same amount of flow was obstructed in this way. The aorta was then clamped above the celiac artery, and the pressure rose to 154 mm.

In another instance clamping the renal, superior mesenteric and celiac arteries and the aorta below the kidneys gave a value of 147 mm. of mercury and clamping

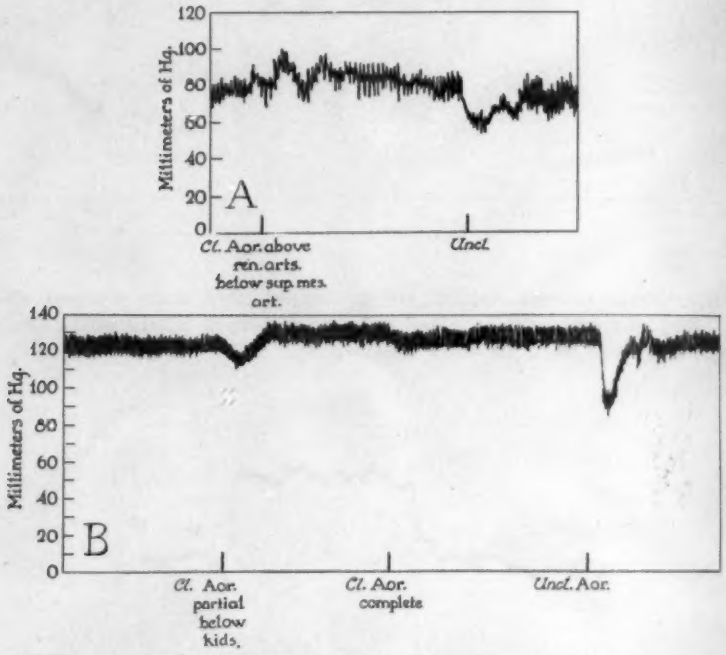

Fig. 5.—*A*, clamping of the aorta above the renal arteries but below the superior mesenteric artery, with release of the clamp after a short interval. *B*, the aorta was clamped below the kidneys and the clamp later released.

the aorta above the celiac artery raised it to 155 mm. In another case the values were 140 and 148 mm. of mercury. The difference was undoubtedly due to flow from the small branches of the aorta between the two levels clamped, the small branch flow being occluded by the upper but not by the lower clamp.

In another experiment the aorta was clamped above the celiac axis. Then the branches of the aorta below that level were clamped one by one. As would be expected, the curve was not influenced by this clamping of the branches, since the branches were distal to the first clamp applied, nor did the pressure fall on release of the clamps from them.

28. Longcope, W. T., and McClintock, A.: Arch. Int. Med. **6**:437, 1910.

Stenosis and then complete closure of the aorta above the kidneys but below the superior mesenteric artery were performed (fig. 5 *A*). The rise was rapid but small, averaging 14.3 mm. of mercury in seven experiments. It was greatest with complete closure of the aorta. Release of the clamp gave a sudden drop with return to approximately the original level. With both renal pedicles tied off, a similar rise and fall were obtained.

Stenosis and complete closure of the aorta immediately below both kidneys caused a rapid but small rise of blood pressure, with a sudden fall on release of the clamp. With the renal pedicles ligated a similar result was obtained. The average rise in 10 experiments was 8 mm. of mercury (fig. 5 *B*).

These values show that the greatest rise comes from obstruction of the aorta above the origin of the celiac artery.

Levy and Blalock [24] gave the value of 18.5 per cent of the output of the left side of the heart for the flow through the kidneys. This was obtained by allowing the flow from the renal veins to pass by a special cannula [29] to a beaker. The rate of flow was then calculated from the

TABLE 2.—*Percentage of Blood Flow Obstructed at the Different Levels and Average Rises of Blood Pressure Produced (See Fig. 1)*

Level of Stenosis	Percentage of Flow Obstructed (Levy and Blalock [24])*	Av. Rise, Mm. Hg	Experiments
1. Above celiac	A + B + C = 60%	56	19
2. Above kidneys	B + C = 31.5%	14.3	7
3. Below kidneys	C = 13%	8.0	10

* A signifies liver and portal bed; B, kidneys; C, lower part of trunk and lower extremities.

time it took for 50 cc. of blood to flow into the beaker. However, the renal flow as determined by Van Slyke and his co-workers [30] varied from 0.2 to 1 cc. per gram of kidney per minute. This is a great range, and it may be that flow in the kidneys was at a lower level than 18.5 per cent when the experiments described here were performed. This may explain the relatively low rise of 14.3 mm. obtained by stenosis just above the kidneys. It is also possible that the stream was partially diverted into the celiac and superior mesenteric vessels.

It seems from the experiments described that obstruction of the aorta, partial or complete, at a level above the origin of the celiac artery gives elevation of the blood pressure to values which are called hypertension clinically. It is believed that this elevation is mechanical for the following reasons:

1. The amount of rise in blood pressure is roughly proportional to the amount of blood flow obstructed.

29. Mason, M. F.; Blalock, A., and Harrison, R.: Am. J. Physiol. **118**:667, 1936.

30. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A. S.: Am. J. Physiol. **109**:336, 1934.

2. The greater the degree of stenosis, the greater the rise in blood pressure.

3. The rise is rapid, occurring within a few heartbeats; the fall, immediate. The formation of a pressor substance in the kidney and its release, with resulting instigation of hypertension, could not occur so quickly.

4. Ligature or clamping of the renal circulation does not affect the nature or the quantity of the rise or fall. (Therefore ischemia of the kidneys is not the cause of the acute hypertension which was obtained.)

5. These rises are not prevented by section of the vagus nerves or by the asphyxia due to pneumothorax.

6. They seem independent of a carotid sinus or other nervous reflex, even the shape of the blood pressure curve being uninfluenced by changes of flow in the common carotid artery.

COMMENT

The amount of the blood flow obstructed in the experiments just described is almost as great as that obstructed in coarctation of the aorta of the adult type, since only the intercostal arteries arise between the celiac and the left subclavian artery. The experiments are therefore comparable to coarctation of the aorta as regards the amount of the circulation obstructed.

The rise of blood pressure caused by complete obstruction of the aorta at a level just above the kidneys amounted to only 14.3 mm. of mercury on the average. Further, complete occlusion of the renal circulation by ligation of the pedicles gave no rise. These facts make it very unlikely that the clamping above the origin of the celiac artery caused acute hypertension by renal ischemia, for the clamp above the kidneys and below the superior mesenteric artery caused as much renal ischemia but only a small rise in blood pressure.

The hypertension due to stenosis of the aorta just above the kidneys in *chronic* experiments by Goldblatt and Kahn [18] and Rytand,[19a] on the other hand, is of quite another nature. In Goldblatt's experiments the rise was gradual, taking several hours to occur and was due to renal ischemia (decreased blood flow to the kidneys), for as soon as collateral circulation becomes sufficient to supply the kidneys adequately the hypertension decreases or disappears. He stated: [6]

> . . . in the animals with the aorta constricted above the origin of both main renal arteries there has been a much greater tendency to return to the original level. In these in order to make the hypertension persist it has been found necessary also to constrict the aorta *below* the renal arteries. Despite this additional procedure the accessory circulation to the kidney appears to be adequate to interfere with persistence of the hypertension at a high level.

This shows that it is necessary to "isolate" the kidney to maintain the hypertension obtained by ischemia of the kidneys.

In coarctation of the aorta the stenosis or occlusion of the aorta occurs just distal to the origin of the left subclavian artery. Thus below this obstruction all of the intercostal arteries (if necessary) are available to allow anastomosis between the subclavian and the internal mammary arteries and the aorta distal to the stenosis but proximal to the origin of the renal vessels. Anastomosis to the inferior epigastric vessels by way of the internal mammary arteries is also available, so that blood could be supplied to the lower part of the body in that way. Clinically one seldom finds the latter,[1b] for the upper routes usually are more than adequate.

The systolic arterial pressure is usually within normal limits in the lower extremities; Abbott [1b] stated that in coarctation the diastolic pressure throughout the body is unchanged.

Hamilton [31] by direct optical blood pressure tracings made simultaneously in a case of coarctation showed pressures above the coarctation to be 160 systolic and 88 diastolic (mean, 113) and pressures below the stricture to be 105 systolic and 82 diastolic (mean, 93). Furthermore, Blumgart and his co-workers [32] found that the oxygen content of the femoral artery and the arteriovenous difference in the lower extremity in cases of coarctation of the aorta were within normal limits. This indicates that patients with coarctation of the aorta have both sufficient oxygen and sufficient arterial pressure in the aorta to insure a normal supply of blood to the kidneys.

If it is true that the diastolic pressure is not increased in coarctation of the aorta, this is an argument against the action of a pressor substance, since pressor substances, such as epinephrine, act by increasing both systolic and diastolic pressures.

Lewis [5] stated that . . . in normal persons the cross sectional area of the ascending aorta, and the total cross sectional area of all the vessels into which it divides before it comes into the descending aorta, are much the same. In coarctation he said,

> If we add together the cross sectional areas of all the branches and include with these the cross sectional area of the isthmus, we again arrive at a total value for the outlet. This value is usually less [5 of 7 cases], sometimes conspicuously, than the value for the cross section of the ascending aorta; but it is almost always greater than the value for the total outlet in the control series. . . . One source of error causes relative underestimation of the values for cases of coarctation during life, for the method fails to take into account the unusual stretching that occurs in many

31. Hamilton, W. F.; Murphy, E. E., and Woodbury, R. A.: Proc. Am. Physiol. Soc., 1939, p. 106.

32. Blumgart, H. L.; Lawrence, J. S., and Ernstene, A. C.: Arch. Int. Med. 47:806, 1931.

of the cases from the high blood pressure within the arteries. . . . the values for the outgoing branches may be too great, because the size of an unbranching vessel may decrease as it proceeds on its course. Thus, it is sometimes erroneous to use the cross sectional area of the innominate artery . . . because the vessel often participates in ballooning of the aorta. [He adds,] It is just possible that . . . the loss occasioned to the outlet by constriction of the isthmus is compensated at that level of the arterial tree by the increased size of the remaining vessels, and continues to be compensated similarly in the branches which go to form collaterals.

Thus, if at present we ascribe the high pressure in the upper part of the body to diminished size of outlet, we cannot do so upon the basis of anatomical evidence; the belief is to be based rather upon a process of exclusion since increased tone of arterioles in the affected territory is apparently not the cause.

Lewis has failed in the foregoing consideration to regard two facts. First, he measured only the large vessels. Therefore it is dangerous to assume that "the loss occasioned to the outlet . . . continues to be compensated similarly in the branches which go to form collaterals" until some one has actually measured them. Second, the resistance in tubes varies inversely as the fourth power of the radius, while cross sections vary only as the second power. Thus it might be possible to have many small tubes (vessels) whose total cross section added to that of the large vessels and the isthmus would give a normal total value, while the resistance they offered could be exceedingly high. It should be further emphasized that the anastomotic vessels are long and tortuous. This, too, increases the resistance. Actually, instead of passing from the heart directly down the descending aorta, in coarctation the blood is forced to go chiefly by way of the anastomoses between the branches of the subclavian and the aortic intercostal arteries.

It is my impression that the obstruction at the isthmus produces hypertension in a manner similar to that of the production of experimental hypertension by constriction of the aorta above the celiac artery and that the elevation is maintained by the resistance of the collateral vessels.

Lewis [5] stated:

. . . the rate at which the pulse wave is conducted in the vessel of the upper limb appears to be greater in the cases of coarctation, presumably owing to the higher blood pressure prevailing in them. Thus, the different time relation between the radial and femoral pulse in normal and in abnormal subjects is due as much or more to early arrival of the pulse at the wrist as to delay in reaching the femoral artery. Since in most instances of coarctation the aorta is incompletely, though greatly, obstructed, pulsation will usually be directly transmitted through the remaining aperture; in other instances it will be transmitted through the partition. Clinically the small lag in the upstroke of the femoral pulse has little significance, for owing to the brevity of the delay it is highly improbable that it could be detected by the unaided senses. . . . in coarctation delay of the femoral pulse is obvious. This palpable delay should not be attributed to delay in the femoral upstroke, but to the slowness with which the pulse rises to and attains its summit. While the average delay of the beginning of the femoral pulse is but 0.03 sec., the

summit has an average lag of 0.145 sec. and this is easily appreciated. The delay . . . may in part be attributable directly to the obstruction just as the summit of the pulse is delayed in stenosis of the aoric valves; it is probably attributable in part to the late receipt of additional waves through large collateral channels.

Abbott [1b] found that the aorta resumes its normal or a diminished caliber at the level of the fourth or fifth intercostal arteries, "which usually take no part in the anastomosis but supply their own district by the blood which reaches them through the aorta" by way of the anastomoses to the first, second and third intercostal arteries. Lewis' description of the pulse at the femoral artery and the blood pressures found in the lower extremities by Abbott [1b] and Blackford [2] indicate that the blood pressure in the aorta distal to the fifth intercostal artery and thus at the kidneys and below is of the same qualitative and quantitative nature as is found with clinical stenosis of the aortic valve. If renal ischemia and the pressor substance resultant from it are present with coarctation of the aorta, renal ischemia must also prevail with stenosis of the aortic valve. With aortic stenosis one would therefore expect the arterioles to be constricted functionally and also to find changes in the eyegrounds. That the eyegrounds are normal clinically is generally known.

Further, while it is true that chronic nephritis and primary hypertension, to which the "renal ischemia" theory seems quite applicable, frequently terminate in death from uremia, such an outcome is rare in stenosis of the aortic valve.

To establish the mechanical factor of the hypertension of coarctation as the principal cause, one must further rule out increase in arteriolar pressure in the head and upper extremities. The experiments described have established the absence of a renal factor. Studies are now quoted to rule out the possibility of arteriolar constriction from other causes.

The early arrival of the pulse impulse at the wrist makes one feel that the heart is contracting forcefully but "blindly" to overcome the resistance offered by the stenosis at the isthmus and by the tortuous anastomoses. If the carotid sinus were stimulated, one would expect a relatively slow pulse rate. "This does not occur, the pulse rate usually being about 70 per minute." [5] However, it is possible that without the carotid sinus effect the pulse would be more rapid.

Lewis [5] stated:

General diminuation or loss of arterial tone would also be anticipated for the same reason. . . . so far as the upper limbs and head and neck are concerned, there is little doubt that loss of tone prevails. Patients with coarctation and high blood pressure have fresh facial coloring. The facial skin is unusually warm to touch. Some patients, when directly questioned about it, speak of suffering from hotness and occasional burning of the face. . . . This pulsation in the cheek, forehead and lips of coarctation patients is remarkably vivid when a glass slide is pressed on skin mucous membrane, rivalling in intensity that seen in free

aortic regurgation. The hands of these patients are unusually warm, even in cold weather, and the palmar surface often shows capillary pulsation over its whole surface. These phenomena all speak for vasodilation, . . . [or easy vasodilation].

Healy, Daley and Sweet [33] on roentgenographic examination found the mandibular canals, the mental foramen and the circulating channels of each tooth prominent in patients with coarctation of the aorta. This speaks for dilated rather than constricted vessels.

Ellis and Weiss,[34] using the histamine flare method of Lewis and Haynal,[35] found the average arteriolar pressure of normal subjects to be 55 mm. of mercury, that of patients with arterial hypertension 108 mm., and that of patients with senile arteriosclerosis 48 mm.

Blumgart and his co-workers,[32] using the method of Lewis and Haynal [35] and Ellis and Weiss,[34] found that in 2 patients with coarctation of the aorta the arteriolar pressure over the sternum was 50 mm. of mercury (normal). This is the point usually used in determining arteriolar pressure by this method. The arteriolar pressure in the upper arm and in the upper part of the thigh was also normal in both. Blumgart and his co-workers [32] therefore stated:

> This suggests that while increased peripheral resistance may be responsible, as in essential hypertension, for the arterial hypertension above the coarctation, this increased resistance is not due to arteriolar resistance but rather to the resistance offered by the constricted aorta and the collateral pathways.

SUMMARY

Coarctation of the aorta is described as observed in 5 adults. The condition was diagnosed in 3 of them during life.

An experiment is presented in which acute hypertension was produced by stenosis or occlusion of the aorta at a level above the origin of the celiac artery. The hypertension experimentally produced is shown to be independent of the kidneys.

The similarity of this acute experimental hypertension to that accompanying coarctation of the aorta in adults is discussed, and further clinical and experimental evidence is pointed out to show that the hypertension associated with coarctation of the aorta is also due to mechanical obstruction and not to renal ischemia with its "pressor substance."

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33. Healy, J. C.; Daley, F. H., and Sweet, M. H.: Apollonian **11**:167, 1936.
34. Ellis, L. B., and Weiss, S.: J. Clin. Investigation **8**:47, 1929.
35. Lewis, T., and Haynal, I.: Heart **14**:177, 1928.

HISTOLOGIC CHANGES FOLLOWING VASCULAR SPASM IN CENTRAL NERVOUS SYSTEM (PITRESSIN EPISODES)

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The previous and present day studies (clinical as well as experimental) of vascular spasm, with its deleterious consequences, are usually concerned with well pronounced clinical symptoms or grossly seen pathologic changes. As Petersen and Milliken [1] stated:

> We are accustomed to regard the blood supply to the tissues as uniformly adequate unless gross pathological disturbances exist . . . in general we assume that in the normal individual all tissues are adequately supplied and clinically we seldom consider the possibility of regional or organ inadequacy of vascular function unless the clinical manifestations are obvious, as in Raynaud's disease.

The so-called functional diseases are so designated because of the lack of detectable lesions of tissue. Minute tissue changes are usually considered "insignificant." Nevertheless, there is much in the way of clinical evidence that makes it probable that in the so-called functional diseases the difficulty may actually reside in the transient periods of inadequate vascularization (due either to undue vessel spasm or undue dilatation of the vascular bed). The possibility exists that such minute functional vascular episodes if prolonged or repeated may ultimately lead to the establishment of permanent lesions, with clinical impairment of function of the involved region or organ of the body. Ophthalmoplegic migraine may serve as a characteristic example, or the transition from transient familial paralysis to spinal muscular atrophy.

EARLY CHANGES

Pitressin (betahypophamine) injected into an animal causes transient vascular spasm of the arterioles and of the capillary bed in different organs and organ systems. Though its action is most pronounced in the gastrointestinal tract, the other organs and systems may also be involved. The reason why in one group of animals the heart is more frequently

From the Department of Pathology, Bacteriology and Public Health, University of Illinois College of Medicine.

1. Petersen, W. F., and Milliken, M. E.: The Patient and the Weather: II. Autonomic Dysintegration, Ann Arbor, Mich., Edwards Brothers, Inc., 1934, pt. 2, p. 4.

involved, in others, the stomach, and so on, is not yet clear. But experimental observations of pressor episodes evoked by injections of pitressin which I have carried on for a period of six years indicate that there are definite seasonal differences and possibly changes in the reactivity from year to year. In certain seasons and years I was most successful in the production of endocarditis (Nedzel [2]); in others, in the production of gastric ulcers (Nedzel [3]). The same is true for the production of lesions in the liver and the kidney (unpublished observations). The transient spasms also render the vascular endothelium more permeable for the passage of micro-organisms and alter the status of the blood vessels so that localization may occur, as, for instance, in the central nervous system (Nedzel [4]).

It is well known that because of inherent anatomic differences a transient vascular spasm is not so readily induced in the central nervous system, but some animals, particularly dogs and rabbits, respond in this way. In the particular experiments to be presented, dogs were used throughout.

EXPERIMENTS

After an intravenous injection of pitressin of 4 units or more per kilogram, most of the dogs reacted by manifestations of involvement of the gastrointestinal tract; i. e., they either vomited or defecated. Only a small percentage reacted by manifestations of gross involvement of the central nervous system, i. e., by dizziness, loss of coordination and even loss of consciousness (with actual collapse). These symptoms are quite transient, lasting usually for several minutes and rarely as long as twenty minutes.

In this paper we are interested in presenting the histologic observations made after single and repeated pitressin episodes when animals were killed from one and a half to thirty hours after the first injection.

The experiments were conducted in the following manner:

Animals received single and repeated injections of the pitressin and were killed in one and one-half (dog 1), two and one-half (dog 2), four and one-half (dog 3), six (dog 4), seven (dog 5) and thirty (dog 6) hours. Dog 1, killed in one and one-half hours, received one injection of pitressin; dog 2 (two and one-half hours), two injections; dog 3 (four and one-half hours), three injections, dog 4 (six hours), four injections; dog 5 (seven hours), five injections, and dog 6 (thirty hours,), nine injections. The dose of pitressin was 20 pressor units per 5 Kg. of weight of the animal.

After the animals were killed, specimens were obtained from the central nervous system and studied. Different areas of the brain, medulla and other parts revealed changes; in the spinal cord, however, the changes were more pronounced

2. Nedzel, A. J.: Arch. Path. **24**:143, 1937.

3. Nedzel, A. J.: Arch. Path. **26**:988, 1938.

4. Nedzel, A. J.: Proc. Soc. Exper. Biol. & Med. **34**:239, 1936.

and consistent, and it was more convenient to study them. In this first paper of the series, the changes observed in the spinal cord are recorded.

Dog 1 (one injection of pitressin; killed in one and one-half hours). This animal revealed definite pathologic alterations. The following changes were noted: There was slight gliosis. The blood vessels were often dilated and congested. Minute hemorrhages (fig. 1 *A*) were frequently observed. In the capillaries (fig. 1 *B*) the endothelium appeared swollen; the lumen of the vessels

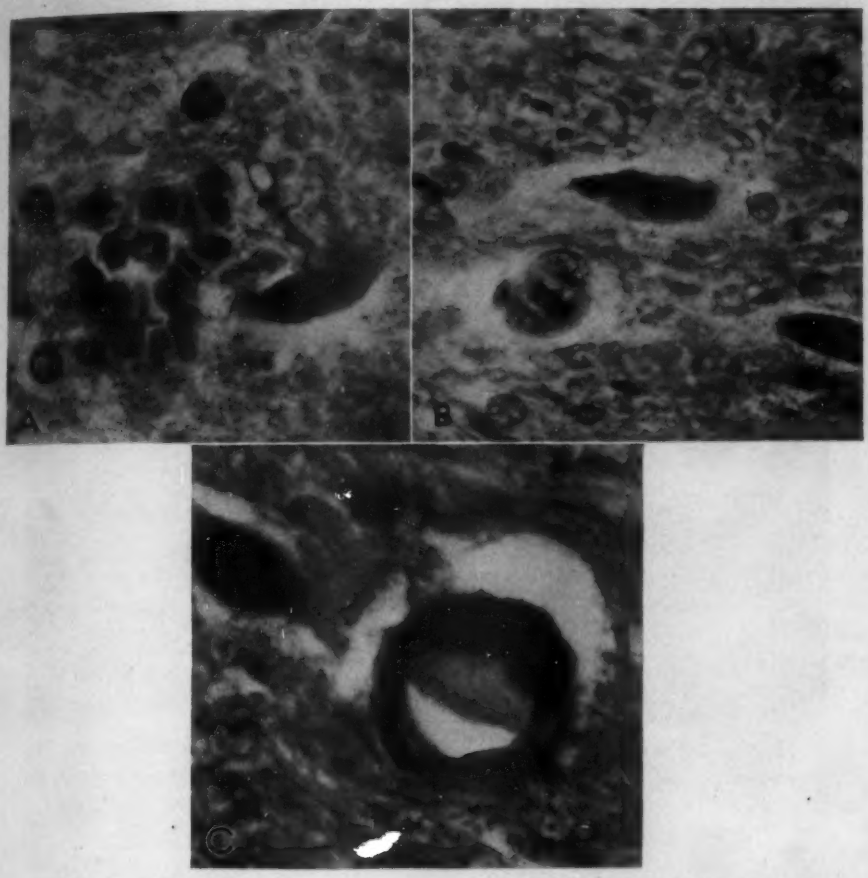


Fig. 1.—*A*, hemorrhage in the gray matter of the brain; hematoxylin and eosin; × 1,100; oil immersion. *B*, swollen endothelium; capillary plugged by leukocyte in fibrin; surrounding edema including the neuron; hematoxylin and eosin; × 850; oil immersion. *C*, lumen of a vessel in the gray matter, partly occluded by fibrin, showing two leukocytes adherent to the wall; hematoxylin and eosin; × 1,145; oil immersion.

was frequently plugged by leukocytes embedded in the fibrin. The tissues around appeared somewhat edematous. An accumulation of leukocytes, with half of the lumen closed by fibrin, was observed, the leukocytes closely adhering to the wall

(fig. 1 *C*). An initial stage of neuronophagia can be recorded (fig. 2 *A*), and an accumulation of glial cells was noted around some of the blood vessels (fig. 2 *B*). Occasionally swelling of axons and myelin sheaths as well as an uneven edema of the gray matter became evident.

Dog 2 (two injections; killed in two and one-half hours). The evidence of gliosis was more pronounced. There were accumulations of glial cells around some of the blood vessels, together with endothelial proliferation. In a widely dilated blood vessel fibrin was found extending from an endothelial layer (fig. 3) (sticky and permeable endothelium), and a few polymorphonuclear leukocytes were embedded in the fibrin (white stasis). Glial cells appeared to have accumulated around the vessel. In another widely dilated blood vessel (fig. 4) the lumen was

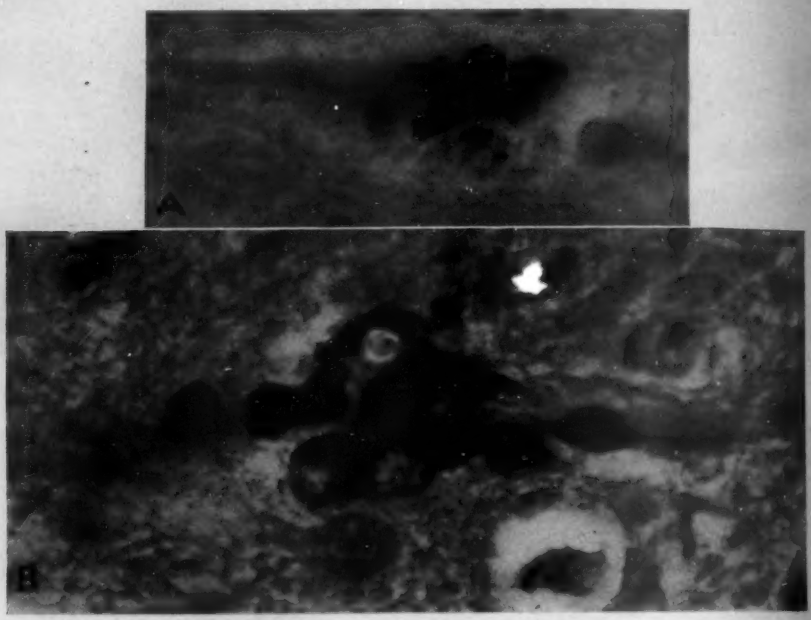


Fig. 2.—*A*, neuronophagia; hematoxylin and eosin; × 1,150; oil immersion. *B*, accumulation of glial cells around a blood vessel in the gray matter; hematoxylin and eosin; × 1,145; oil immersion.

largely filled with fibrin and platelets. There were shadows of erythrocytes, practically all adhering to the lower wall of the vessel. A considerable number of leukocytes, mostly polymorphonuclear, were found scattered in the fibrin and also adherent to the vessel walls, and a few of them had passed out of the lumen (below to the left). Neuronophagia and shrinkage of the nerve cells in the gray matter were noted, and the axons and myelin sheaths were found swollen in some of the fields.

Dog 3 (three injections; killed in four and one-half hours). The swelling of the myelin sheaths and axons, as well as fenestration, was pronounced, and occasionally polymorphonuclears were noted in the gray matter. Proliferation of the endothelial cells with the polymorphonuclear leukocytes in the capillary

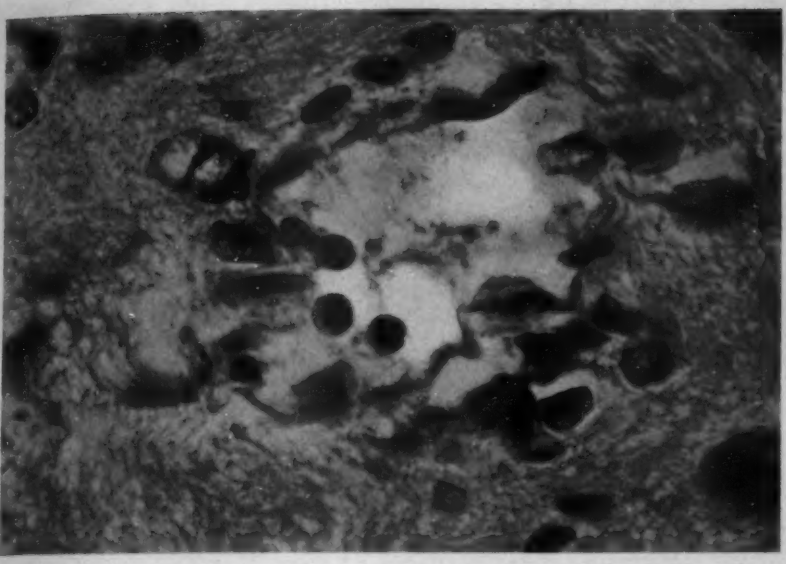


Fig. 3.—Greatly dilated vessel in the gray matter, filled with fibrin, platelets and some erythrocytes; swelling of the endothelial cells; two polymorphonuclears in the center of the field, with an accumulation of glial cells; hematoxylin and eosin; × 795; oil immersion.

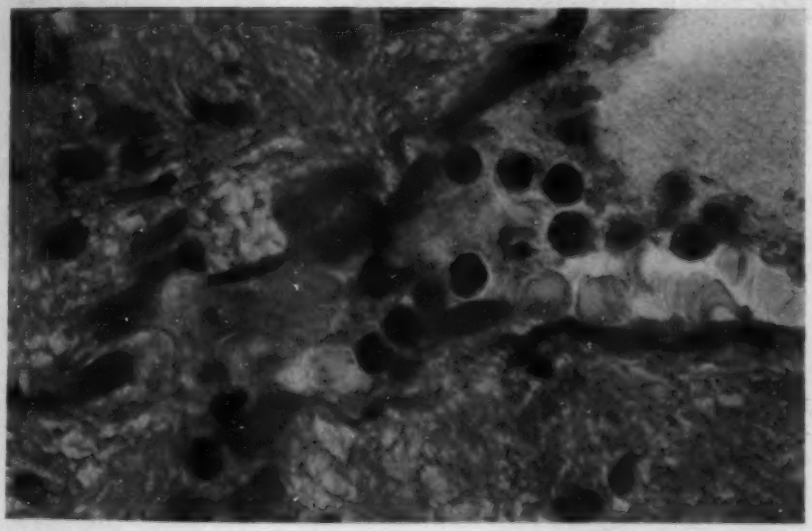


Fig. 4.—Widely dilated vessel with fibrin and platelets closing the lumen; many mononuclears and polymorphonuclears, two of which are extravascular (below and to the left); hematoxylin and eosin; × 779; oil immersion.

was observed (fig. 5 *A*). Near the border of the gray matter, in the white matter about a closed vessel (fig. 5 *B*) a considerable number of glia cells were aggregated. Many small thrombotic blood vessels were observed, and in figure 6 *A* two of these are seen in the same field. The one on the left is closed by fibrin, while the one on the right contains a hyalin-like mass. Between them can be seen small parts of a swelling axon and myelin sheaths. In figure 6 *B* there is shown

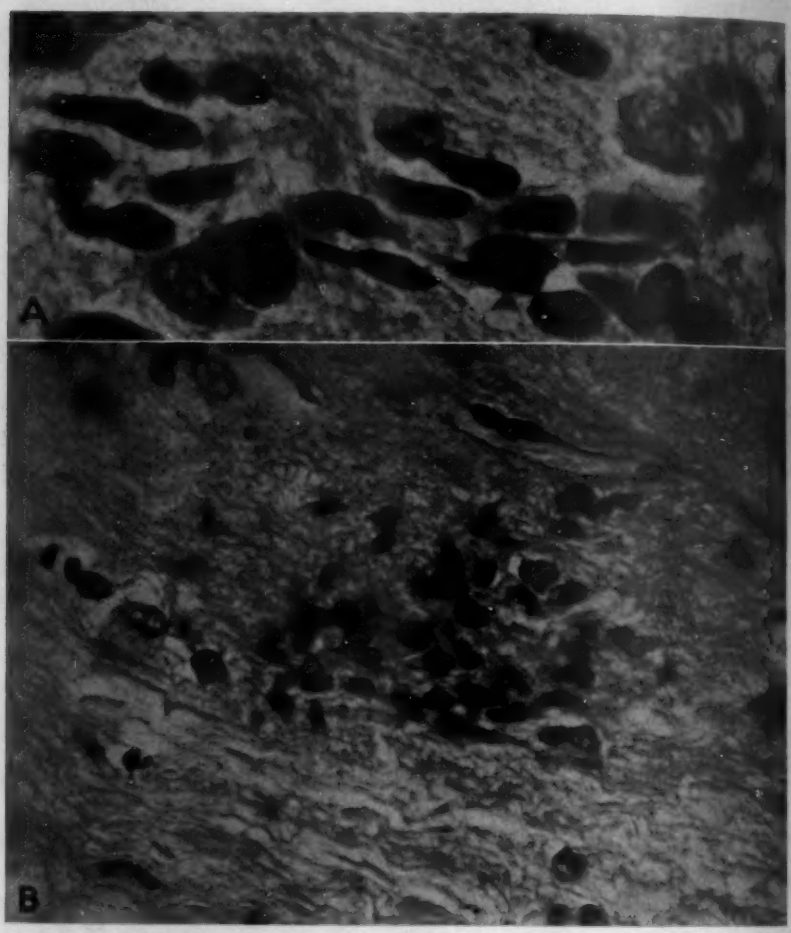


Fig. 5.—*A*, proliferation of endothelial cells with glial accumulation; two polymorphonuclear leukocytes in the capillary; hematoxylin and eosin; × 1,024.4; oil immersion. *B*, white matter showing in the center occluded blood vessels and a conglomeration of glial cells; hematoxylin and eosin; × 805; oil immersion.

an almost completely hyalinized thrombus in which two mononuclear cells have been engulfed.

Dog 4 (four injections; killed in six hours). In the sections there were marked gliosis, swelling of the endothelium in some of the capillaries and hyalinized

thrombi together with proliferation of the blood vessels and polymorphonuclears. There were karyorrhexis in the gray matter, neuronophagia, and varicosities and beading of the capillaries, more noted in the white matter. Droplets of fat (sudan staining) were present near the central canal, and minute droplets were observed occasionally in the nerve cells and in the endothelial cells of the blood vessels. Many axons and myelin sheaths were swollen, and fenestration was pronounced.

Dog 5 (five injections; killed in seven hours). The changes were similar to those observed in dog 4. The capillary endothelium was unusually swollen. Some of the blood vessels in the white matter were well surrounded by glial cells,

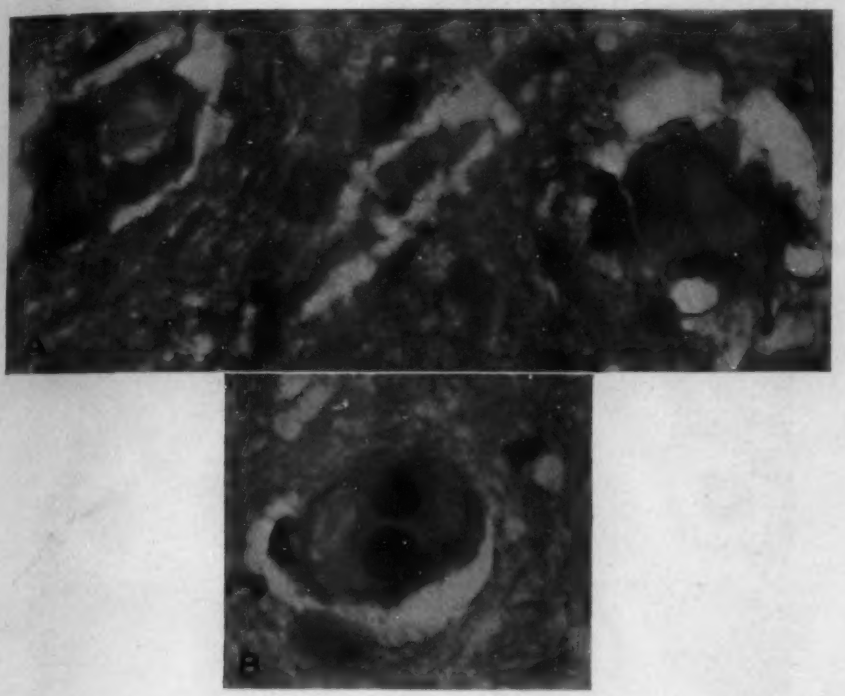


Fig. 6.—*A*, two small thrombotic vessels in the white matter—the one to the left with fibrin, the one to the right with a hyalinized thrombus; in the intermediate zone, swollen axons and myelin sheaths; hematoxylin and eosin; × 1,145; oil immersion. *B*, thrombotic venule containing two mononuclear cells in the gray matter; hematoxylin and eosin; × 1,145; oil immersion.

and here the presence of fat droplets was more pronounced. As is shown in figure 7, small fat droplets were noted in the nuclei of a nerve cell (*A*), in the cytoplasm (*B*) and then engulfed in the phagocytic cells and carried in the direction of the blood vessels (*C*). Finally they could be observed in the wall of a blood vessel, apparently being transferred to the lumen (*D*).

Dog 6 (seven injections; killed in thirty hours). Similar but more pronounced changes were observed. Gliosis was more pronounced, and mitosis was observed occasionally. The nerve cells near the blood vessels were shrunken and deformed,

with corkscrew-like dendrites (fig. 8*A*). Swollen axons and myelin sheaths were scattered in patches over the slide (fig. 8*B*). Some of the blood vessels in the white matter appeared twisted, varicose and beaded.

COMMENT

It is readily apparent that the spasm of the small vessels evoked by pitressin (corresponding to the ARS phase of Petersen) is followed by a restorative phase (COD phase). The more prolonged the ARS phase, the more manifest the COD phase. The ARS phases, depending

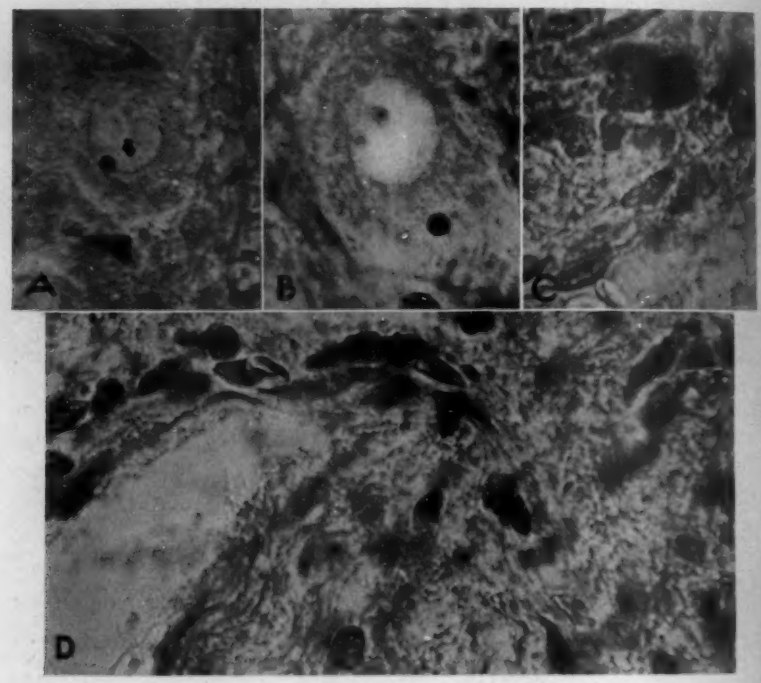


Fig. 7.—*A*, small fat droplet in a nucleus; *B*, small fat droplet in cytoplasm; *C*, phagocytic cells loaded with fat droplets near a blood vessel; *D*, droplets of fat in capillary walls; sudan III; × 900; oil immersion.

on their degree and duration, do not pass harmlessly. The incidental regional anoxia damages the tissue to such an extent that alterations can be observed microscopically, leaving out of consideration well known clinical functional manifestations. Pathologic changes, as can be seen, are intimately connected with the blood vessels and, of course, actually make their appearance in the changed status of the blood vessels themselves. First, the endothelium of the capillaries becomes swollen, adhesive and permeable; second, small hemorrhages appear. The leuko-

cytes (mostly polymorphonuclear) reveal an increase in number; glial cells accumulate among the blood vessels; the perivascular spaces and tissues around the blood vessels become edematous. Later thrombotic blood vessels are observed, with thrombi composed largely of fibrin, which later becomes hyalinized. In some of these thrombi leukocytes

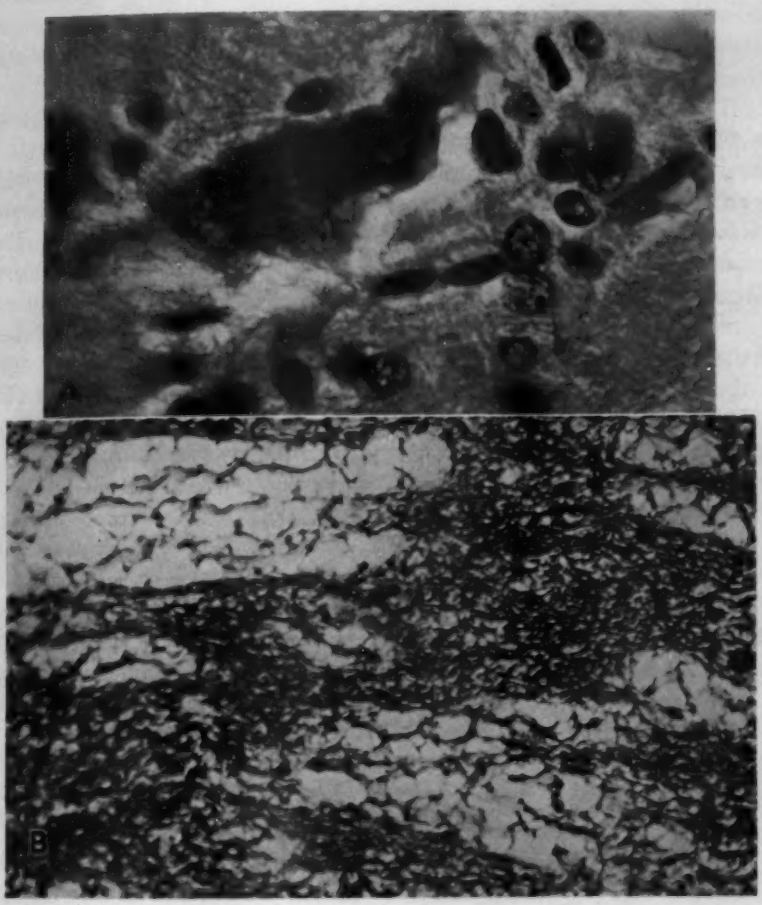


Fig. 8.—*A*, nerve cell with shrinking dendrite, corkscrew form; closed capillary with accumulation of glial cells; hematoxylin and eosin; × 900; oil immersion. B, swollen axons and myelin sheaths, scattered in patchlike form. Weil's myelin sheath stain; × 300; dry.

are engulfed. Swollen myelin sheaths and axons are found in scattered patches. The location of these patches is obviously to be connected with the blood vessels which appear to be most altered in function as well as in histologic appearance. Gliosis appears more and more pro-

nounced, closely following the increasing and continuing vascular spasm. Definite changes occur in the nerve cells, appearing in a range from simple hydration to necrobiosis, manifested by the appearance of fat droplets, the shrinking and twisting of the fibrils and finally the neuronophagia. These degenerating and degenerated cells are not damaged *en masse* and are not localized in certain definite regions, but are widely scattered. Here, too, in most instances these groups or these singly damaged nerve cells are most often found where the blood vessels also show the greatest alterations and abnormalities.

It seems logical to assume that if exaggerated spasm of the blood vessels can cause such visible changes in the spinal cord without the animal showing definite prolonged clinical symptoms, persons with unstable vascular systems who reveal only transient clinical symptoms involving the central nervous system will presumably also have similar microscopic lesions. Any number of factors—emotional excitement, remote trauma, infection, undue exercise and particularly meteorologic alterations—which may occasion pressor episodes in the vascular bed of the central nervous system may lead to definite pathologic changes in the tissue of the type herein described, but it must be evident that under normal conditions these relatively evanescent histologic alterations would be rapidly repaired and the picture restored to normalcy.

I have been primarily interested in presenting these seemingly minor alterations that can be observed in the tissues of the central nervous system after injections of pitressin because of the implication that normally occurring pressor episodes will be followed by similar alterations and that these will be accentuated in the person in whom vascular alterations are already present, in the person who has an unstable vasomotor system and in certain persons domiciled under unusually unstable environmental conditions, which subject the vasomotor control to wide demands for adjustment.

LATER CHANGES

It has been shown here that transient vascular spasms evoked by injections of pitressin induce definite, microscopically demonstrable pathologic changes in the tissues. There are recorded minute hemorrhages, swelling of capillary endothelium and thrombus formation in blood vessels. Leukocytes accumulate in the blood vessels, and there is perivascular accumulation of glial cells. In some instances nodule-like aggregations of glial cells, capillary endothelial proliferation and patchy swelling of axons and myelin sheaths can be observed. Varicose and beaded blood vessels are also seen. Nerve cells reveal partial disintegration; neuronophagia is present, and fat droplets are formed in nerve cells, are picked up by phagocytic cells and are carried to the blood vessels.

Now, I shall present histologic alterations in the spinal cords of the dogs which were given injections of pitressin once a week for a period of over one year. The dose was so adjusted that the reaction of the animals to the injected drug was satisfactory, the animal responding visibly in one way or another, namely, by profuse salivation, defecation, urination, loss of equilibrium or consciousness, and so on. If the dog did not show any of the aforementioned reactions after the injection, the succeeding dose was increased. In time tolerance to pitressin developed, and to produce a comparable effect the dose had to be increased.

It is of interest that the same animals which react well to a definite dose and then become refractory for one or two periods may again, with succeeding injections, reveal the normal effect. In animal 7 there were constant responses to the usual dose, so later ones were decreased to half, and the same results were obtained. For about three weeks during March 1937 this dose proved sufficient, but later it was necessary to resume the usual dose and finally even double and triple it. This animal, and also animal 9, during the first half of April 1938 had had their dose tripled, in comparison with the initial one; then suddenly they began to react so violently that the dose had to be decreased. It also should be mentioned that all the animals reacted to the same doses in different degrees. The most violent reactions were observed in the late winter and spring, while the mildest ones, if any, were noticed in the summer and in the first part of the fall. These findings are in agreement with the previous observations of the action of pitressin in experiments producing endocarditis and gastric ulcer (Nedzel [5]) as well as in studies of the toxicity of certain drugs in different seasons and on different days (Nedzel [6]).

The initial dose of pitressin was 4 units per kilogram of weight of the animal. The animals were put to death and specimens obtained from the central nervous system and examined as recorded in the text.

It was to be expected that the histologic changes would differ from those observed in the acute stages, previously described, since the injections were given continuously, and that the lesions would be more chronic, owing to the persistence of changes caused by the previous injections.

Dog 7 (first injection given Jan. 22, 1937; killed April 20, 1938). During the period of experiment the dog received fifty-nine injections of pitressin. At all times, apart from the immediate effect of the injection of pitressin, this dog appeared to be in a good state of health. When the spinal cord was examined minute hemorrhages and swelling of the capillary endothelium and accumulation

5. Nedzel.[2] Nedzel.[3] Petersen, W. F., and Milliken, M. E.: The Patient and the Weather: III. Mental and Nervous Diseases, Ann Arbor, Mich., Edwards Brothers, Inc., 1934.

6. Nedzel, A. J.: J. Lab. & Clin. Med. **22**:1031 and 1125, 1937; **22**:1063, 1938.

of glial cells were observed. In the white matter blood vessels were widely dilated, and in the adjacent regions there were swelling of axons as well as of myelin sheaths and presence of a considerable number of glial cells perivascularly. Also

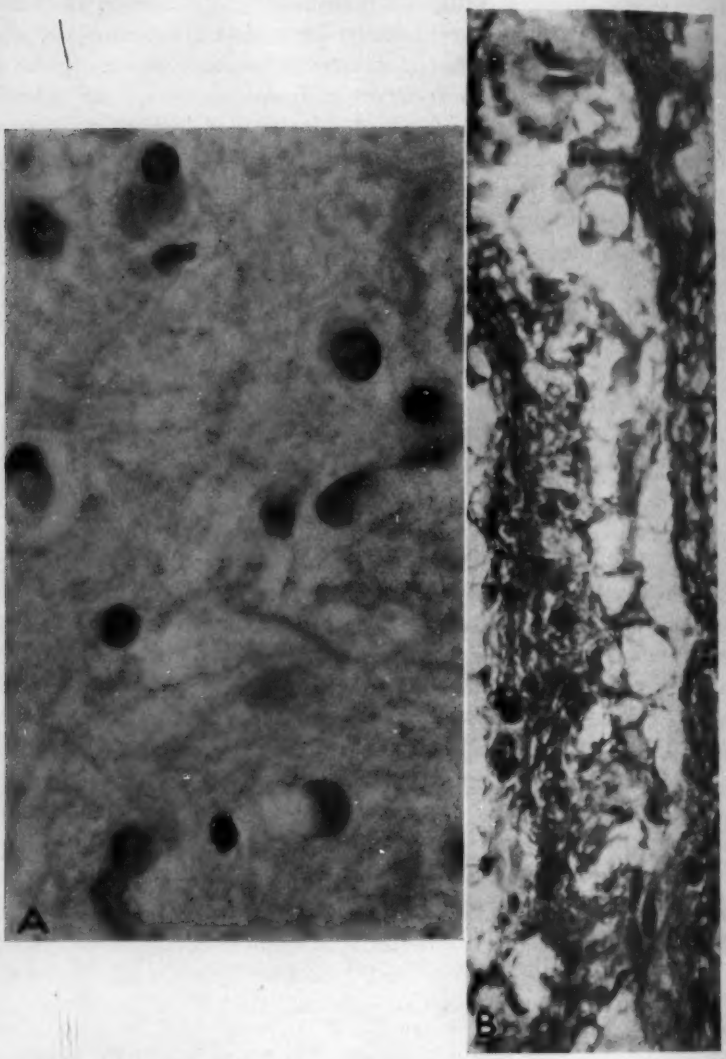


Fig. 9.—*A*, vascularization of the gray matter; gliosis; hematoxylin and eosin; × 1,150; oil immersion. *B*, swollen axon and myelin sheath between two blood vessels to the left in the lower half, gliosis; Weil's myelin sheath stain; × 600; dry.

accumulations of round cells about the capillaries were observed. Here and there neuronophagia of single cells was noted, as well as small accumulations of glial cells.

Dog 8 (initial injection Feb. 11, 1937; died April 4, 1938). The total number of injections was fifty-two. On Jan. 13, 26 and 31, 1938, this animal received a single injection of pitressin, 4 units per kilogram of weight, but hardly reacted; later the dose was increased to 8 units, and this dose was administered seven times. The last two doses were followed by very slight reactions. April 1 the animal received a dose of 12 units per kilogram, and a violent reaction followed. On April 6 and 14 single doses of 6 units per kilogram of weight were given. The reaction on April 6 was well pronounced. After administration of the same dose on April 14 the animal expired in a few minutes. Postmortem examination revealed no gross pathologic changes other than pronounced paleness of the visible mucous

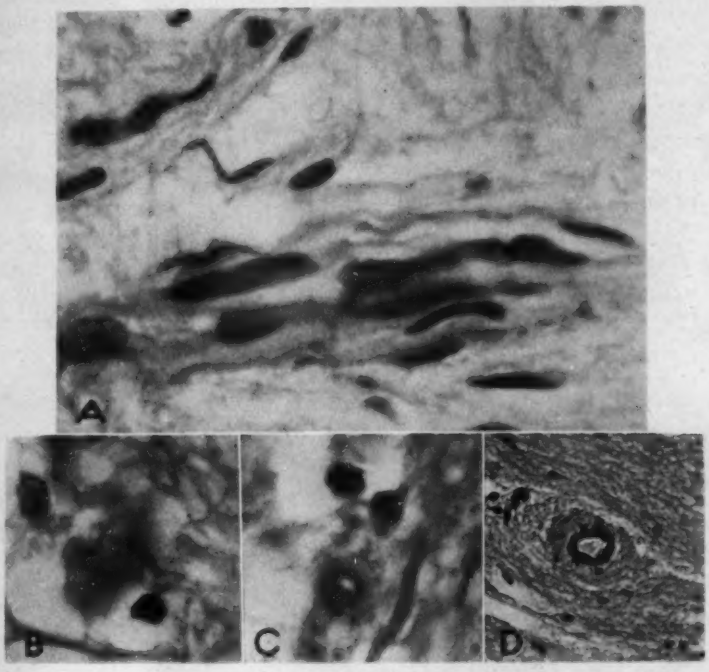


Fig. 10.—*A*, obliterated blood vessel in the white matter; fibrous glial rods; Van Gieson's stain; × 1,150; oil immersion. *B*, obliterated blood vessel; Van Gieson's stain; × 1,150; oil immersion. *C*, two blood vessels with thickened walls; hematoxylin and eosin; × 1,150; oil immersion; *D*, Van Gieson's stain; × 250; dry.

membranes and of the heart, which was markedly contracted and very firm. Microscopically, the changes were similar to those described for dog 7. Leukocytes, largely polymorphonuclear, had accumulated in some of the capillaries, and there were aggregations of glial cells. In some fields well pronounced gliosis with an increased number of capillaries (fig. 9 *A*) could be observed.

Dog 9 (first injection Jan. 22, 1937; killed April 22, 1938). The total number of injections was fifty-nine. Early changes were observed, similar to the ones found in the two previous animals, namely, minute hemorrhages, swelling of capillary endothelium, stasis, edema, accumulations of glial cells in nodule form and around the blood vessels, occasional neuronophagia of single nerve cells,

scattered here and there, regional gliosis and other changes. In addition to this, the specimen from this animal revealed swollen axons with swollen myelin sheaths, well defined, in patchlike form. Figure 9 *B* represents swelling of an axon and of its myelin sheath located exactly between two small blood vessels. Disorganized capillaries which were being gradually replaced by fibrous glial

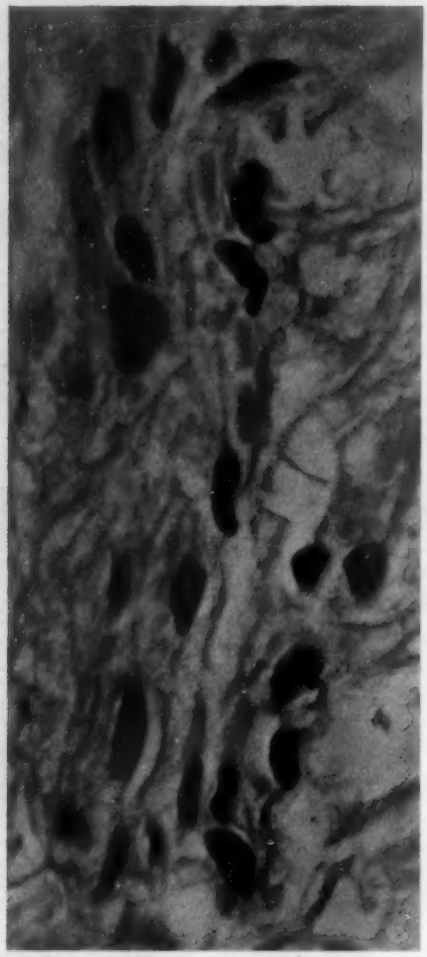


Fig. 11.—Accumulation of glial cells around a blood vessel; endothelial deterioration; hematoxylin and eosin; × 1,150; oil immersion.

cells (rods) (fig. 10 *A*) were observed, and a capillary (fig. 11) had been undergoing changes in which its endothelial nuclei became twisted, and different types of glial cells were accumulating. There were also two blood vessels with highly thickened walls (not swollen), as shown in figure 10 (*C* and *D*), and also an obliterated small blood vessel (*B*).

COMMENT

These alterations are, most of them, similar to the ones described previously. Nevertheless, there are some new ones which should be attributed to the repetition of injections of pitressin over a longer period of time. These are the appearance of thickening of blood vessel walls, not resulting from mere swelling of endothelial cells, as in the initial changes, and the appearance of fibrous glial cells in more abundant numbers. These are practically always observed in close proximity to or in intimate connection with the small blood vessels. It is to be assumed that the limited number of such small lesions of chronic type speaks for itself. It shows, in the first place, how readily the nerve tissues of the dog combat the minute changes inflicted by vascular spasm by restoring the injured tissue to the normal state. Secondly, it shows that if one wishes to produce a condition simulating that presumably present in a sensitive human being one will have to provoke vascular spasms with pitressin more frequently and for a longer period of time, thus simulating what occurs naturally in northern latitudes, which lie in the path of constantly and radically shifting meteorologic effects (Petersen [7]). Experimentation in this direction is in progress.

SUMMARY

Transient vascular spasms induced by injections of pitressin cause definite changes in the central nervous system which can be observed histologically. The early changes consist of swelling of the endothelium of the capillaries and the appearance of small hemorrhages. The leukocytes (mostly polymorphonuclear) increase in number, glial cells accumulate among the blood vessels, the perivascular spaces and tissues around the blood vessels become edematous. Later thrombotic blood vessels are observed, with thrombi composed largely of fibrin, which later becomes hyalinized. In some of these thrombi leukocytes are engulfed. Swollen myelin sheaths and axons are found in scattered patches. Gliosis is noted, and definite changes occur in the nerve cells appearing in a range from simple hydration to necrobiosis, manifested by the appearance of fat droplets, shrinking and twisting of the fibrils, to final neuronophagia. If the spasms are induced through a longer period of time, some new findings may be obtained. These are thickening of blood vessel walls, not resulting from mere swelling of endothelial cells as in initial changes, and the appearance of fibrous glial cells in more abundant numbers.

7. Petersen, W. F.: The Patient and the Weather: I. The Footprint of Asclepius, Ann Arbor, Mich., Edwards Brothers, Inc., 1935, pt. 1.

Case Reports

CARCINOID OF STOMACH

ALFRED PLAUT, M.D., NEW YORK

In a postmortem examination of the organs of a 69 year old diabetic woman there was felt on the lesser curvature of the stomach, 7 cm. from the cardia, a small, firm, ovoid, slightly raised nodule. Its cut surface (after overnight fixation in solution of formaldehyde U. S. P.) was grayish white and measured 3 by 1.5 mm. The nature of this nodule was not recognized in the gross specimen; microscopically, it turned out to be a typical carcinoid. It seems unnecessary to repeat the description of such a tumor. There was no doubt about the diagnosis; Dr. Masson concurred.

There were in this autopsy several other interesting observations, which, however, I shall not attempt to correlate with the carcinoid. The woman was obese and had a mustache at the angles of the mouth. The pancreas was atrophic and fibrous, and one ovary contained a granulosa cell tumor, 7 by 5 mm. The adrenal cortex was markedly hyperplastic; the thyroid gland, slightly so. Aside from the rare tumor, the stomach was not remarkable.

No attempts were made to demonstrate argentaffine granules in the carcinoid. The hope of finding them was almost nil, judging from the condition of the material.

Carcinoid of the stomach is little mentioned in the literature. In the textbooks of pathology, one generally does not find it mentioned at all. In some books and papers carcinoid is briefly described as rarely occurring in the stomach. Considering the possibility that carcinoid of the stomach might have been described under other diagnoses, I have searched the literature. I did not find tumors recorded which I could recognize as carcinoids, either from the microscopic pictures given or from the descriptions, under the heading of sarcoma of the stomach, endothelioma of the stomach or benign tumor of the stomach. In many case reports, notably those of older date, it is impossible to decide whether or not the tumor described might have been a carcinoid.

No carcinoid of the stomach was found mentioned among the tumors described by Krompecher and others as basal cell carcinoma of the stomach.

The following cases of small carcinoids of the stomach, discovered accidentally at autopsy, were found recorded in the literature:

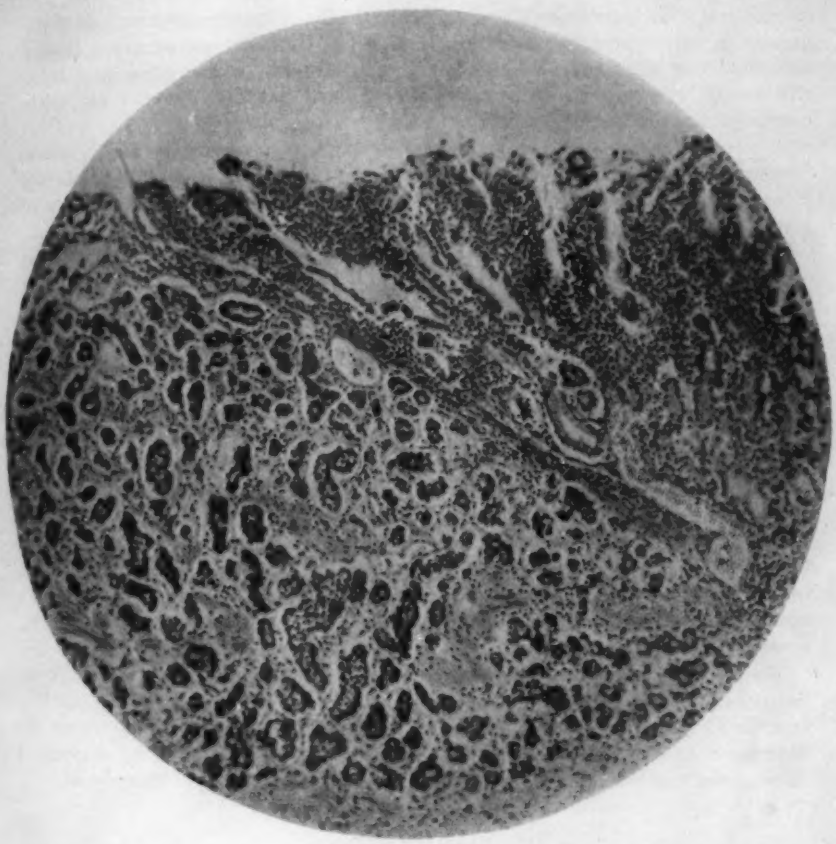
1. Askanazy's [1] first case. In the musculature of the stomach, 2 mm. above the pylorus, a carcinoid was found, measuring 0.5 mm. in diameter. The mucosa over it contained a polyp. The patient, a woman 80 years of age, had died of bronchopneumonia. There is no statement concerning a connection of the tumor with the mucosa.

From the Department of Pathology, Beth Israel Hospital.

1. Askanazy, M.: Deutsche med. Wchnschr. **49**:49, 1923.

2. Askanazy's second case. The tumor was found in a man 89 years old who had died of cystopyelitis resulting from hypertrophy of the prostate. The nodule measured 11 by 7 by 2 mm. and was situated mainly in the submucosa, extending a little into the mucosa. There is no statement about the location in the stomach.

3. Paltauf's [2] case. The carcinoid was a well circumscribed, lentil-sized nodule in the mucosa of the stomach of a woman 64 years old. No further data are available.



Carcinoid of the stomach. There is postmortem change in the mucosa. The tumor has separated the bundles of the muscularis mucosae.

4. Feyrter's [3] first case. In a woman of 66 years a nodule, larger than a lentil, was situated in the submucosa and a small part also in the mucosa. It formed a shallow protrusion with a central depression. At its lower edge a small, thin-walled vein was found entirely filled with tumor. No data are given on other observations at autopsy.

2. Paltauf: Zentralbl. f. Path. **48**:234, 1930.

3. Feyrter, F.: Ergebn. d. allg. Path. u. path. Anat. **29**:305, 1934.

5. Feyrter's second case. A roughly pea-sized nodule was situated in the fundus of the stomach of a man 56 years old. It formed a button-like yellow protrusion. This tumor also was situated mainly in the submucosa, partly in the mucosa.

6. Walley's [4] case. The tumor reported occupies an intermediate position between these small typical carcinoids and the larger atypical ones which made clinical symptoms. It was found on gastroscopic examination in a man 41 years old who, among many other symptoms, had had epigastric pain for years. Removal of the tumor did not alter the epigastric pain. This carcinoid formed a polypoid mass, 1 cm. in diameter, which projected into the lumen on the posterior wall of the greater curvature near the sphincter antri. From the histologic structure, Walley concluded that the tumor was similar to a carcinoid. A silver stain gave negative results. From the low power photomicrograph Walley gave I am fairly convinced that his tumor was a carcinoid.

There are three other reports on carcinoid of the stomach in the literature. The cases, however, are different from the present case as well as from the 6 cases just mentioned. The reports are concerned with gastric tumors that caused severe clinical symptoms.

Raiford [5] reported the case of a man 55 years old who for ten months had had vague attacks of indigestion and had lost 15 pounds (6.8 Kg.) in weight. At laparotomy metastases were found in the liver and lymph nodes. The patient died a few days later. The microscopic picture was that of a carcinoid. No special stains were employed. Dr. Geschickter gave me the opportunity of studying one of the slides, and I feel also that we were dealing with a somewhat atypical carcinoid.

Pettinari [6] reported the case of a 47 year old carpenter whose previous history was irrelevant, especially as far as the gastrointestinal tract was concerned. For three months he had had epigastric pain with regurgitation and anorexia but without pyrosis. At operation an ovoid tumefaction, the size of a large nut, was found in the pyloric region, which had created an absolute pyloric stenosis. The serosa and the mucosa over the tumor were perfectly normal. This tumor was histologically considered carcinoid by Pettinari and also by Pepere. Argentaffine cells were found in small numbers. From the histologic pictures given, I cannot convince myself absolutely that one is dealing here with a carcinoid. It might, however, be atypical carcinoid.

Finally, Entwisle [7] removed 5 polypoid tumors, up to 2.8 cm. diameter, from the stomach of a 25 year old schoolteacher, a woman, who had had a previous appendectomy for repeated attacks of abdominal pain and vomiting. From the description of the microscopic picture and from the slide put at my disposal, I cannot form a definite opinion concerning this tumor. It might be a carcinoid.

COMMENT

There is little to say in the way of comment. The main purpose of this report is to draw the attention of pathologists to the occurrence of the small, harmless carcinoid in the stomach. It is not known why the carcinoid is so rarely found in the stomach. The argentaffine cells, from which the carcinoid originates, occur in the stomach in large numbers (Hamperl [8]).

4. Walley, G. I.: St. Barth. Hosp. J. **44**:141, 1937.

5. Raiford, T. S.: Am. J. Cancer **18**:803, 1933.

6. Pettinari, V.: Arch. ital. di chir. **40**:695, 1935.

7. Entwisle, R. M.: Pennsylvania M. J. **40**:1026, 1937.

8. Hamperl, H.: Zentralbl. f. Path. (supp.) **40**:171, 1927.

While the figures available are too small for any statistical purposes, it is worth while to mention that the six reports on small carcinoids in the stomach concerned old people (80, 89, 64, 66, 56 and 69 years old). The ages of the patients who had clinical symptoms from their atypical carcinoids were 41, 55, 47 and 25. The question of the age incidence of carcinoids in general is unsettled as far as my knowledge of the literature goes.

SUMMARY

A case of carcinoid of the stomach found accidentally at autopsy is added to the few similar cases reported in the literature. All the tumors of this type reported have been found in old people.

PRIMARY INTRAMEDULLARY NEUROFIBROMA OF THE HUMERUS

PAUL GROSS, M.D.; FRANK R. BAILEY, M.D., AND HAROLD W. JACOX, M.D., PITTSBURGH

While neurogenic sarcoma primary in soft tissues occasionally involves bone,[1] only a single case, recorded by Peers,[2] has been found in which neurogenic sarcoma was primary in bone. It was considered that the probable origin of this tumor was "from one of the sparse nerve trunks within the marrow cavity of the ulna," and on cytologic grounds it was thought to be of low grade malignancy.

It is our purpose now to report the occurrence of the benign counterpart, apparently the first to be recorded in the literature, of the primary intramedullary neurogenic sarcoma.

REPORT OF A CASE

A white housewife, aged 30, had been aware of a lump on the outer aspect of the left arm for about three years. This was associated occasionally with localized sharp pains but more commonly with a dull ache radiating down the arm to the fingers. The lump, discovered accidentally, increased only slightly in size but gave more trouble during the fourth pregnancy, which terminated normally seven weeks before the patient's admission to the hospital. She was in good health, and the past history was noncontributory. Her mother had died of cancer of the stomach.

The patient was a normal adult white woman with a hard, fixed, tender mass attached to the lateral aspect of the middle third of the left arm. There was no evidence of generalized neurofibromatosis.

A roentgenogram (*A* in the figure) showed a comma-shaped cystic lesion within the middle third of the left humerus, about 2 by 1 by 1 cm. in size. The cortex was thickened and broken in one place, with small irregular areas of calcification in the adjacent soft tissues. At the lower edge of the tumor there was a reactive triangle of periosteum and bone, suggesting the possibility of a malignant change. But the general appearance was that of a benign tumor that might have existed three years.

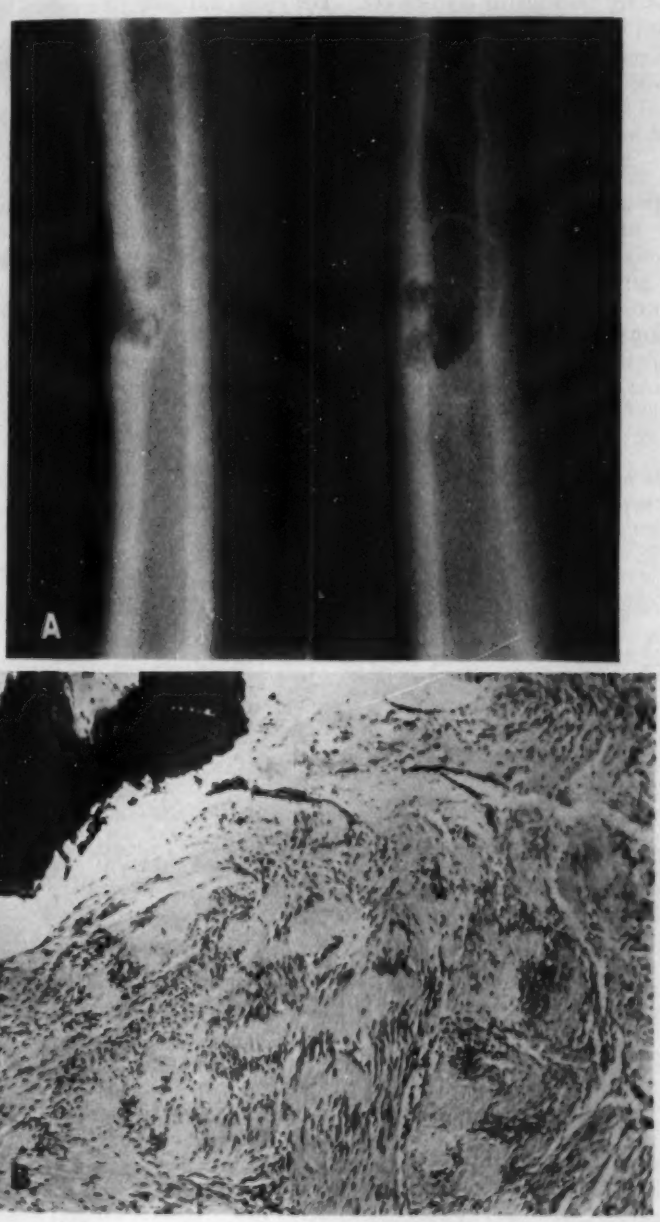
With the patient under ether anesthesia, an exploration was made, which disclosed a soft, fleshy, reddish gray, well encapsulated bone tumor, about 2 by 1 by 1 cm., apparently arising from the medulla of the middle third of the humerus. It was in close contact with but not attached to the radial nerve, which had to be retracted to permit removal of the tumor with the surrounding dense bone.

From the Western Pennsylvania Hospital.

1. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone (Including the Jaws and Joints), New York, American Journal of Cancer, 1936.

2. Peers, J. H.: Am. J. Path. **10**:811, 1934.

The patient made an uneventful recovery and was discharged on the third postoperative day. Since then she has had no further trouble with the arm, and roentgenograms have shown complete healing.



A, anteroposterior and lateral roentgenograms of the intramedullary neurofibroma of the humerus. *B*, photomicrograph of the intramedullary neurofibroma; hematoxylin and eosin; × 105. Cancellous bone is seen in the upper right corner.

As received in the laboratory, the tumor was a well encapsulated, pink-gray, ovoid, soft mass, 2.5 by 1 by 1 cm., to the periphery of which spicules of bone were adherent. Resistance to the knife was slight. The cut surface bulged and was faintly fasciculated and smooth. The color was pale yellow-brown, mottled by small hemorrhages, which were confluent in one area.

Microscopically, the tissue showed the palisading of nuclei and fibrillae characteristic of the neurofibroma (perineurial fibroblastoma, schwannoma) (*B* in the figure). Neither the cellularity nor the appearance of the nuclei gave any suggestion of malignant change.

COMMENT

Clinically and roentgenographically, the diagnosis was difficult. The rarity of the lesion precluded the possibility of diagnosing the tumor correctly. The bone changes demonstrated in the roentgenogram indicated an intramedullary origin of the neoplasm and were not those of a pressure defect. Peers [2] pointed out that in most textbooks of histology mention is made of nerve fibers in bone, usually accompanying vessels. The origin of the intramedullary neurofibroma, like the neurogenic sarcoma described by Peers,[2] from such a nerve appears probable.

SUMMARY

An intramedullary neurofibroma of the humerus, apparently the first to be reported, is described.

General Reviews

ACCEPTED AND DISPUTED CONCEPTS IN THE PATHOLOGY OF PULMONARY TUBERCULOSIS

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The most intense controversies today over the genesis of pulmonary tuberculosis center on the unsolved questions of endogenous and exogenous infection in reinfection type tuberculosis, the reasons for racial difference in the severity of the disease, the character of primary tuberculosis as it occurs in adults, and the relation of allergy and "immunity" to the resistance displayed in the course of the disease. In the succeeding pages chief attention will be given to these problems, but an attempt will be made to fit them into a larger picture including the problems of etiology, the question of the portal of entry and other issues relating to reinfection tuberculosis. Finally an attempt will be made to estimate the factors decisive for the course of pulmonary tuberculosis, as they appear from the main facts at hand.

ETIOLOGY

There is relatively little dispute over the etiology of pulmonary tuberculosis. All lesions can be explained without difficulty as due to the well known tubercle bacillus. It is now generally admitted that the bacillus may be present in granular and nonacid-fast forms, as well as in the typical acid-fast rodlike shape, but studies of the micro-organism in artificial culture indicate that such forms for the most part represent phases in growth and are not to be considered as true variants from the common acid-fast bacillus.

On the subject of filtrability of the bacillus there is more debate, but the majority of students of the problem oppose the view that the etiologic agent of tuberculosis may exist in a virus-like form, capable of passing the pores of standard laboratory filters suitable for such a test.

From the Henry Phipps Institute, University of Pennsylvania.

The Annual Conversational Lecture delivered before the Pathological Society of Philadelphia, April 13, 1939.

Within recent years colony variation in artificial culture has become a well known fact, and differences have been shown to occur in the type of disease produced experimentally by the bacilli from "rough" and "smooth" ("R" and "S") colonies of the organism. The significance of these laboratory findings for human pathology is, however, not yet clear.

The bacillus causing human pulmonary tuberculosis is almost always of the human type. The bovine type is becoming increasingly rare in this country as a cause of any form of tuberculosis.[1] It has never been of any significance as a cause of pulmonary tuberculosis, although cases of infection of the lungs by the bovine bacillus are occasionally reported abroad, where the incidence may be as high as 4 per cent.[2] No accepted case of avian bacillus infection has been reported in this country (for discussion see Feldman [3]).

PORTAL OF ENTRY

The primary portal of entry of the tubercle bacillus for pulmonary tuberculosis appears most commonly to be the lung itself. In the early history of exact investigation of tuberculosis the view of von Behring that the disease in man as well as in cattle is chiefly alimentary in origin was widely accepted. A school of French students, under the influence of Calmette, still adhere to this view. Most pathologists, however, accept the conclusions of Ghon, who investigated the matter meticulously and rarely failed to find an original focus in the lung, presumably aerogenic, regardless of the location and extent of subsequent spread. Blacklock,[4] who recently restudied the problem, with a large amount of material at his disposal, substantiated Ghon's contention in summarizing his own investigations with the conclusion that "from pathological, histological and bacteriological points of view the primary lesion would appear to be due to direct infection of the lungs through the air passages."

The remarks just made apply specifically to primary infection. The problem of reinfection tuberculosis is much more complicated. The origin of this type of tuberculosis, the characteristic disease of adults, is the subject of continued argument as will be indicated in the following paragraphs.

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1. Van Es, L., and Martin, H. M.: The Incidence of Avian Tuberculosis in Mammals Other Than Swine, Research Bulletin 49, University of Nebraska College of Agriculture, Agricultural Experiment Station, 1930, p. 1.

2. Griffith, A. S., and Monro, W. T.: J. Path. & Bact. **35**:271, 1932.

3. Feldman, W. H.: Avian Tuberculosis Infections, Baltimore, Williams & Wilkins Company, 1938.

4. Blacklock, J. W. S.: Tuberculous Disease in Children: Its Pathology and Bacteriology, Medical Research Council, Special Report Series, no. 172, London, His Majesty's Stationery Office, 1932.

INFECTION, LATENCY AND REINFECTION

Investigators are generally agreed that in the genesis of the ordinary pulmonary tuberculosis of adult life a period of latency, varying from a few months to many years, occurs between the original infection and the ultimate progressive disease. The two types of tuberculosis thus separated by a period of latency are of fundamentally different anatomic character. In former years primary infection was very common in early childhood, and the period of latency was the succeeding years of childhood, adolescence and early adult life. All mortality statistics have shown the years from 4 to 14 almost free from fatal tuberculosis. Explanations for the relative freedom from serious tuberculosis during this period vary, and space will not be taken to discuss them here.

The subsequent tuberculosis, the "phthisis" of adolescent and adult life, is of disputed origin. Investigators agree that it represents superimposed infection of some sort, but are divided as to whether the infecting bacilli of the new form of tuberculosis come from old latent lesions within the body, i. e., old residues of the first infection, or from the respiratory discharge of another infected person. The new type is commonly called reinfection, superinfection or adult type tuberculosis. All these terms are subject to objections. The term "reinvasion tuberculosis" would seem more suitable.

PRIMARY TUBERCULOSIS

The question of primary, or first infection, tuberculosis must be discussed under two heads, viz., as it occurs in children and as it is seen in adolescents or adults. The distinction is of the utmost importance at the present time because of the increasingly frequent escape of the child from tuberculous infection and the corresponding increasingly common occurrence of first infection after the childhood years have passed.

In Childhood.—The character of first infection tuberculosis in childhood is well understood. Few would disagree with the definition in "Diagnostic Standards" of the National Tuberculosis Association, in which the disease is described as characterized by a single or rarely multiple parenchymal lesion, usually in the lower or middle part of the lung, with secondary involvement of the hilar lymph nodes, commonly regressing by encapsulation and calcification but occasionally progressing by lymphatic and hematogenous dissemination. All agree that the association of infiltration in the lung and enlargement of the tracheobronchial lymph nodes is characteristic; the two lesions together, following the original terminology of Ranke, are often called the primary complex.

The clinical course is usually benign. The child may not appear at all sick or may have the symptoms of an ordinary cold. The lesion as

seen in the roentgen film, consisting of clouding of a pulmonary field and enlargement of the hilar shadow, tends gradually to become smaller. Ultimately, after many months or a few years, one or more dense spots are left in the pulmonary field and in the hilar lymph nodes. As anatomic examination proves, these represent calcified nodules.

Occasionally, more commonly in colored than in white children, the lesion is progressive, the involvement of the lymphatic structures increases and a caseous node softens, with discharge of its contents into the bronchial tree or into the vascular system. The result in the first case is tuberculous pneumonia and in the second case generalized tuberculosis.

In Adolescent and Adult Life.—Primary tuberculosis in adolescents and adults is far less well understood. It is the subject of much present day discussion, for apparently it is becoming increasingly frequent. The subject is of such importance that it was made one of the main problems for discussion at the last meeting of the International Union Against Tuberculosis. It must be admitted, however, that in the individual case there is much difficulty in determining whether a lesion under consideration is primary or not. Its original course cannot be observed anatomically for obvious reasons, and can be studied only in roentgen films. The criteria for primary tuberculosis are not simple. Absence of the shadows of old calcified tubercles does not exclude previous tuberculosis, for the lesions of old primary tuberculosis are visible in only a fifth or at the most a third of patients known to be or to have been infected. The usual criterion for freedom from previous infection is a negative tuberculin test, but it is becoming increasingly clear that the lesions of old primary infection may heal so thoroughly that the positive response to tuberculin is lost. Thus a tuberculous process developing in an adult who has previously been negative to tuberculin may represent simply a new infection in a person who has lost his sensitiveness from an old one. This fact may have a bearing on the dispute over the whole nature of primary tuberculosis in adults, although it may not simplify the problem. Aronson [5] has seen 2 interesting instances of new infection of clinical significance develop in tuberculin-negative children with old evidence of tuberculosis in the form of childhood nodules, in one of which the new lesion had the anatomic characteristics of primary, or childhood type, tuberculosis and in the other, of reinfection, or adult type, tuberculosis. Such cases permit some conclusions, but one has no idea how many "fresh infections" developing in a person with a negative reaction to tuberculin and with a normal roentgen film, and on that basis considered primary, are in reality reinfections occurring in a person

5. Aronson, J. D.: Unpublished data.

previously infected but so slightly that no evidence of previous infection is visible, in whom the reaction to tuberculin has become negative through gradual loss of sensitiveness.

Rival investigators differ with respect to both the pathologic and the clinical character of first infection in the post childhood years. As yet there has been no systematic investigation from the point of view of pathologic anatomy. Many individual observations and opinions, however, are on record and the result is great confusion. Obviously, the opportunity for study by the usual methods of morbid anatomy is extremely limited, depending on chance deaths from other causes than tuberculosis. Hence, in reality, most of the claims for one or another type of pathologic character are based on roentgen examination of the living subject.

There has been an abundance of examination from the clinical point of view, and opinions have been expressed with definitiveness and strongly. However, they do not agree. Present opinions as respects both the pathologic anatomy and the clinical course of primary tuberculosis in adults may be divided conveniently as follows: 1. The process is anatomically similar to that occurring in childhood but apt to follow a progressive rather than a benign course. 2. The process is both anatomically different and clinically more malignant. 3. The process is anatomically similar to that in childhood and clinically relatively benign, differing in no significant respect from first infection as it occurs commonly in young children. 4. The process is anatomically different but has the same benign clinical character as first infection in children.

The first view is the oldest one. In the past much was written on the serious effect of primary tuberculous infection in adults, particularly first infection as it occurred in primitive peoples coming from regions free from tuberculosis to heavily infected environments. As late as 1924 Aschoff [6] expressed the current view in the following words: "We must remember that with the prevention of the primary infection in childhood the adult is sent forth into life unprotected against this disease, which will then attack him with infinitely greater virulence than the usual familial infection in infancy." Heimbeck,[7] who wrote of an excessive morbidity in nurses first exposed to tuberculosis during their training, is perhaps the leading exponent of this view today, but many other writers recently have reported cases of rapidly progressive primary tuberculosis in adolescents.

The second view has been pressed in this country particularly by Sweany,[8] who has described the pathologic peculiarities of first infection

6. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

7. Heimbeck, J.: Arch. Int. Med. **47**:901, 1931.

8. Sweany, H. C.: Am. Rev. Tuberc. **39**:236, 1939.

in adults as follows: The infection tends to occur in the upper part of the lung, just as does reinfection tuberculosis in adults, and to remain confined to the parenchyma of the lung, with relatively little involvement of the hilar lymph nodes, in contrast to the rule in childhood. Moreover, unlike the childhood lesions, the primary pulmonary infiltrations of adult life tend to soften and ulcerate, and if they regress show less tendency to calcify. Indeed, Sweany has held the view that much of the adult tuberculosis commonly supposed to be of the reinfection type is in reality progressive primary tuberculosis.

The third view has been stated repeatedly in this country by Myers and colleagues,[9] who have summarized their experience as follows:

> . . . adults in whom the first infection type of tuberculosis develops, even with considerable involvement in the pulmonary parenchyma and regional lymph nodes, do not require treatment in any form. . . .
>
> Apparently it makes little or no difference at what time of life the first infection with tubercle bacilli occurs, with reference to the evolution of tuberculosis in the human body. When the first infection type of disease occurs in the second and third decades of life, it is just as benign as when it occurs in childhood.

Anatomic support for this view is found in the experience of Terplan,[10] who reported typical regressing cheesy primary complexes in men and women as late as the seventh decade of life.

Fourthly and finally one comes to the view that first infection in adults is usually clinically benign but that in anatomic character it approaches reinfection, or adult type, tuberculosis. Writing with regard to the differential diagnosis of primary and reinfection tuberculosis, Opie[11] said, "Unfortunately, with regard to its recognition during life, tuberculosis of first infection affects the apices with increasing frequency in adolescence and adult life." Myers[12] himself, while stressing the mildness of the clinical course, published roentgen films illustrating apical onset of first infection tuberculosis, rather similar to reinfection type in this respect. Scheel,[13] who was selected to present the problem of primary infection in adult life at the 1937 meeting of the International Union Against Tuberculosis, stated that first infection in adult life, although it often gives rise to clinical manifestations, is usually benign. In his experience the changes in the hilar lymph nodes were less characteristic than those in first infection in childhood, and less commonly

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9. Myers, J. A.; Diehl, H. S.; Boynton, R. E., and Trach, B.: Arch. Int. Med. **59**:1, 1937.

10. Terplan, K. L.: Am. Rev. Tuberc. **29**:77, 1934.

11. Opie, E. L.: Am. Rev. Tuberc. **32**:617, 1935.

12. Myers, J. A.: Tuberculosis Among Children and Young Adults, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

13. Scheel, O., in Report of the Tenth Conference of the International Union Against Tuberculosis, Lisbon, 1937, p. 213.

recognizable. Redeker,[14] in discussing the paper, stated that in Germany only rarely in adults did he see the typical primary intrapulmonary infiltration regressing to a hard nodule, i. e., the usual sequence in primary infection in childhood.

Thus the matter of primary tuberculosis in late life is far from clear. Much further observation is needed before agreement is likely to be reached. For more extended consideration, the reader is referred to a review of the subject by Soper and Amberson.[15] One may conclude for the present by recognizing as an inescapable epidemiologic fact that, with the nationwide postponement of primary infection characteristic of the present decade, no wave of malignant primary tuberculosis is apparent.

REINFECTION TUBERCULOSIS

There is general agreement on the anatomic character and course of so-called reinfection tuberculosis, the type responsible for at least 90 per cent of all deaths from tuberculosis and 5 per cent of deaths from any cause. It is defined briefly in "Diagnostic Standards" of the National Tuberculosis Association as a disease characterized by parenchymal infiltration, usually of the upper third of the lung, without gross involvement of the hilar lymph nodes, retrogressing by resorption and fibrosis or progressing by caseation, softening, excavation and bronchogenic spread. As noted in an earlier paragraph, it occurs after a period of latency following a primary infection. It is relatively rare before adolescence but may occur any time after that, and in modern times it is showing a greater incidence than appears previously to have been the case in the late years of life.

Localization in the Upper Part of the Lung.—One of its most obvious characteristics, never thoroughly explained, is its localization in the upper part of the lung. Formerly, on the basis of pathologic examination the disease was believed to be strictly apical in origin, but in the years since roentgen examination of supposedly healthy adults became common it was discovered that the immediate onset, often progressing abruptly to clinical disease, is commonly subapical or "infraclavicular." For a time students of morbid anatomy, on the one hand, and clinicians, on the other, have disagreed, the former holding out for the truly apical onset and the latter for the subclavicular start. It is now well recognized that progressive and destructive pulmonary tuberculosis passes through, if it does not actually begin with, an acute exudative subapical lesion.[16]

14. Redeker, F., in Report of the Tenth Conference of the International Union Against Tuberculosis, Lisbon, 1937, p. 252.

15. Soper, W. B., and Amberson, J. B.: Am. Rev. Tuberc. **39**:1, 1939.

16. Douglas, B.; Nalbant, J. P., and Pinner, M.: Am. Rev. Tuberc. **31**:162, 1935.

Reconciliation of the views of pathologists and clinicians seems apparent in the work of such men as Pagel,[17] who finds that the first postprimary foci of pulmonary tuberculosis are commonly at the true summit of the lung but that they have a tendency to become inactive, while secondary infraclavicular lesions, derived from the former, can liquefy after a short course, excavate and become the source of extensive bronchogenic spread.

The reason for the localization in the upper part of the lung in reinfection tuberculosis has never been satisfactorily given. Brown[18] indicated the many views in the following statement:

> The relative lack of mobility, the narrow upper thoracic aperture, the shortened and firm first costal cartilage, the possibly ossified first cartilage, the dropping down of the sternal ends of the first ribs, the furrow made by the first rib, the malformed vertebrae, the dwarf-like apical bronchi, the relatively overgrown apex, the gradual accumulation of dust and bacteria in the apical lymphatics, all individually or collectively may play a part in helping to centre tuberculous infection in the apices.

A theory as widely followed as any is that expressed by Tendeloo[19] and others, who claimed that movement of the lung is least in the apical part and that renewal of the air in that part is proportional. According to this view, tubercle bacilli brought in with the inspired air, as well as with the lymph or the blood, are more likely to remain in the apex. Tendeloo stressed the fact that the apex extends more than an inch above the rib cage and is thus largely deprived of the inspiratory pull of the chest muscles. Lurie[20] pointed out, in connection with his animal experiments, that this limitation of motion would make for a piling up of bacilli, which, in turn, might ultimately result in sufficient concentration to overcome the local tissue resistance. This theory fails to explain satisfactorily the difference in the localization of primary and reinfection tuberculosis, and is at variance with the fact that minute foreign particles, as silica dust in pneumonoconiosis, do not tend to accumulate in the apexes but rather in the midlung fields. Indeed writers of note, including Orsos[21] and Loeschke,[22] have built a diametrically opposed theory based on the view that the apexes are the best ventilated portions of the lungs and under the greatest tension. This old dispute is thus far from settled.

Softening and Excavation.—The problem of softening and excavation is not in active debate. Rather it has been relatively neglected, and

17. Pagel, W.: Am. J. M. Sc. **189**:253, 1935.
18. Brown, O. H.: Am. Rev. Tuberc. **7**:120, 1923.
19. Tendeloo, N. P.: Studien über die Ursachen der Lungenkrankheiten, Wiesbaden, J. F. Bergmann, 1902.
20. Lurie, M. B.: Unpublished data.
21. Orsos, F.: Beitr. z. Klin. d. Tuberk. **70**:504, 1928.
22. Loeschke, H., and Dehoff, E.: Ergebn. d. ges. Tuberk.-Forsch. **2**:81, 1931.

strangely so, since it is one of the key problems of tuberculosis. Both caseation and softening are usually, although vaguely, referred to the allergic state of the infected man or animal. The evidence is almost wholly experimental. Pagel [23] found that caseous tissue planted in the subcutaneous tissue of a hypersensitive animal tends to soften, while that planted in a normal animal does not. More recently Lurie [24] demonstrated that the caseous tissue of a tuberculous rabbit behaves like heterologous, not homologous, protein and stimulates the formation of precipitins. The latter are not antibodies to the bacilli present but are specifically related to the protein debris, which must represent modified tissue protein. This seems to be a good lead in the study of the important phenomenon of softening.

Once softening has occurred and communication with a bronchus is established, certain events follow almost inevitably, although they may vary greatly in degree. The cavity itself is inflated and dilated with inspiration, a mechanical factor leading to increasing damage of tissue and local spread of infection. With free drainage established, the opportunity for bronchogenic spread is present, and the well known course leading to the phthisic lung, with excavation and most extensive disease at the top and disease of progressively decreasing severity in the lower parts, is started. Although there is difference of opinion over the importance of mechanical, chemical and other factors in cavity formation, there is general agreement on the results and the cause and nature of bronchogenic tuberculosis.

Endogenous or Exogenous Reinvasion.—The most debated of all problems in the genesis of reinfection pulmonary tuberculosis is the source of the infecting bacilli, in brief, the question whether the infection is endogenous or exogenous. Twenty years ago the endogenous origin was almost universally accepted. The view was current that virtually all people were infected in childhood and that a certain small proportion of these "broke down" as a result of endogenous spread of tubercle bacilli from unhealed foci of childhood infection or the residues of its early extension. The various strains of adult life were believed to be the factors favoring "breakdown," lowering resistance in some way and permitting the release of bacilli from old foci.

Within the last decade, particularly in the United States, the view of exogenous infection probably has become the majority view, and the present antituberculosis campaign has been built largely on the hypothesis of reinfection from outside during adult life.

The leading exponents of the exogenous view in this country have been Opie and McPhedran and Myers. Opie and McPhedran [25]

23. Pagel, W.: Beitr. z. Klin. d. Tuberk. **76**:414, 1931.
24. Lurie, M. B.: Unpublished data.
25. Opie, E. L., and McPhedran, F. M.: Am. Rev. Tuberc. **14**:347, 1926.

showed clearly in an extended study of family groups in Philadelphia, through routine roentgen examination of adults living in close contact with patients who had open tuberculosis, that the former were several times more likely to show both the clinically unrecognizable apical pulmonary infiltrations and also the more grave lesions of adult type tuberculosis than others not living in contact with tuberculous patients, even though each group possessed an equal chance for endogenous reinfection from old, apparently arrested childhood type, tuberculosis. Impressive evidence for exogenous infection was submitted by Opie and McPhedran [26] in the excessive incidence of newly acquired tuberculosis in prevously healthy persons living with tuberculous consorts.

Although the validity of the figures on which this claim for exogenous infection was made, has never been questioned, a swing back toward the endogenous view in this country is now evident. Miller in particular has written extensively on the subject. Much stress is laid on the work of certain investigators abroad. The investigations of Pagel, who well represents the thought of the majority of the German investigators, are widely cited. Pagel [17] found exacerbations of the foci of old primary tuberculosis in about 25 per cent of cases, more frequently in the glandular than in the pulmonary component of the primary complex. He has reported many cases in which careful histologic study appeared to link up reactivity of an old smoldering focus with bronchogenic lymphogenous or hematogenous spread of bacilli, leading eventually to characteristic adult type tuberculosis. Particularly was this the case in the development of the well known "infraclavicular" infiltrations, which, as pointed out already, frequently represent the onset of the reinfection type tuberculosis, and which have been rather generally considered exogenous.

Wallgren,[27] in Sweden, also widely cited, champions the endogenous view on clinical and theoretic grounds rather than as a result of anatomic investigation. According to his conception, "pulmonary tuberculosis is not the immediate result of introduction of tubercle bacilli either from the outside or from the inside . . . but is rather the effect of activity by bacilli which in most cases of pulmonary tuberculosis have long remained in the same place but have not been able to start a progressive process on account of resistance on the part of the organism and particularly the lungs." The school represented by Wallgren lays great stress on constitutional factors such as those related to puberty, pregnancy and the physiologic changes of aging, as responsible for the lowering of resistance.

26. Opie, E. L., and McPhedran, F. M.: Arch. Int. Med. **50**:945, 1932.

27. Wallgren, A.: Acta tuberc. Scandinav. **10**:321, 1936.

A modified conception of endogenous reinfection, taking account of repeated exogenous inoculation, has been proposed. According to this view, tubercle bacilli absorbed into the already infected body through exposure by contact with persons suffering from open tuberculosis, while themselves ineffective in establishing new tuberculous lesions in the face of the existing acquired resistance, enhance allergy and provoke increasingly intense focal reaction in the existing lesions until finally bacilli escape from the latter in large numbers and induce new lesions elsewhere. The mechanism of endogenous release of bacilli under these circumstances has been designated by Redeker and others as the "trigger action of superinfection." The conception has failed to receive much attention in this country. Pathologists and clinicians here as a rule do not see the necessity of such an elaborate mechanism when it is known from a large background of laboratory experiment that fresh inoculations of tubercle bacilli, in doses comparable to those which may be acquired from exposure by contact in man, are capable of setting up new lesions in the face of already existing tuberculosis.

In a careful review of the whole subject Pinner [28] stressed the possibilities of endogenous, without belittling the potentialities of exogenous, reinfection. He pointed out that with proper timing of infection and regulation of dosage very high resistance to exogenous infection can be demonstrated in laboratory animals. That this resistance to invasion from without can be modified by adverse conditions he freely admitted, and in this connection he pointed out that the bulk of statistical evidence for exogenous infection as the cause of typical pulmonary tuberculosis in man has come from study of contact and noncontact populations in underprivileged groups living at a level not far from that of bare subsistence. The reality of endogenous reinfection, on the other hand, as he pointed out, is inescapable in the manifestations of extrapulmonary tuberculosis.

An unbiased analysis of the opposing claims has been made by Rich,[29] who came to the following conclusions, which are conservative and seem to me to be entirely reasonable as a disposition of the subject at present:

> The truth, in all probability, lies in a midposition between these extreme views. There are probably many cases in which tuberculosis arises from the escape of bacilli from latent lesions of primary infection; many cases in which reinfection from without leads to progressive disease in individuals in whom the resistance conferred by a primary infection has become depressed by adverse conditions, and many cases in which the immunizing power of a permanently arrested primary lesion serves to protect the individual from further contact infection.

28. Pinner, M.: J. A. M. A. **107**:475, 1936.

29. Rich, A. R.: Minnesota Med. **21**:745, 1938.

VARIATION WITH RACE AND AGE

The difference in severity of tuberculosis in the white, black, brown and red races has long been discussed. That the mortality from tuberculosis in the colored races is far greater than that in the white race is an inescapable fact. The reason for the difference, however, is the subject of continued argument; one group holds that the tissues of the colored races are inherently less resistant than those of the white race, while an opposing school finds little difference when living conditions are comparable and relates the variation largely to the relatively unfavorable environmental conditions to which the colored races are exposed.

With the views of extremists in each group I need not deal. Conservative investigators accord a role to each factor. That the Negro in this country ordinarily lives at a lower economic level than the white person and in general is more commonly subject to crowding, poor sanitation and inadequate nutrition is not denied, and those who believe that the hereditary factor is important in the Negro's more severe tuberculosis freely admit that greater exposure through contact and environmental conditions injuring resistance is effective in considerable measure in leading to rapidly progressive disease.

The argument for the additional hereditary factor was well presented by Pinner and Kasper,[30] who based conclusions on the results of postmortem examination of approximately 500 Negro and white patients. They stressed particularly the qualitative differences in the character of disease in the two races, pointing to the greater frequency of hematogenous and lymphatic dissemination in the Negro, to the greater tendency toward exudative or caseopneumonic tuberculosis, to the weaker capacity of this race to oppose a fibrous barrier to advancing tuberculous lesions and to other physiologic and anatomic differences that might be correlated with greater susceptibility.

The opposing arguments have been indicated by Opie,[31] who stated conservatively that "the information at hand does not show that the Negro race has any hereditary susceptibility to tuberculosis, but this possibility cannot be excluded." He emphasized dosage of bacilli rather than genotypic differences in relation to the more massive disease of the Negro race, pointing out, on the basis of figures which are not disputed, that Negroes tend to scatter tubercle bacilli in vastly greater numbers, if for shorter periods of time, than white patients with the usual chronic type of tuberculosis, with the result of massive infection and corresponding tendency to propagate disease of the same acute type.

The work and views of numerous others who have considered carefully both sides of the question could be cited. It would seem, however,

30. Pinner, M., and Kasper, J. A.: Am. Rev. Tuberc. **26**:463, 1932.
31. Opie, E. L.: Am. Rev. Tuberc. **22**:603, 1930.

that one can do no more at present than recognize the force of the arguments on each side. The dispute resolves itself largely into an argument between those who admit that environment plays a very important part but insist that heredity plays a part, too, and those who admit the possibility of a hereditary factor but believe that environmental factors are sufficient to explain all the discrepancies now known. Since human conditions can never be perfectly equalized, the problem can probably never be solved through human observation alone. On the other hand, it is quite possible that the question may be settled to general satisfaction, by analogy, through results of well controlled laboratory experiments on different strains of several species of animals.

The problems of age in relation to tuberculosis are somewhat similar to those of race. The relatively acute disease of infancy and of the period of puberty, and the now recognized tendency toward progression in the late years of life of lesions previously held in check, have given rise to arguments of the same sort, in which variation in environment, on the one hand, and variation in constitutional resistance, on the other, are stressed. The correlation of progressive infantile tuberculosis and the opportunity for massive infection from a parent with open tuberculosis is ordinarily so close that little argument is opposed to environment as responsible for the extra severity of the disease in the very young. However, those who believe in the importance of constitutional differences are unwilling to credit the relatively acute disease seen in young adults, particularly women, to difference in exposure from the periods just preceding and just following young adulthood. Nor are they willing to concede lightly to environmental factors alone the "break" that appears to occur in old age. It would not be profitable to follow at length the arguments of both sides. For a comprehensive consideration of the various factors concerned one may well turn to the article by Rich,[29] already cited, "The Influence of Age-Determined Factors on the Development of Tuberculosis." A good case is made out for the importance of constitutional factors, although it is apparent that constitution itself is modified by environment and that a sharp distinction cannot be made between the two. At least, however, the greater severity of tuberculosis in the youthful patient does not seem ordinarily correlated with greater doses of infecting bacilli. Nor does the apparent increase in tuberculosis in the aged seem to be explainable on this ground. As a rule the old are less heavily exposed. Obviously, observations of opposite import, from crowded groups in asylums, poorhouses and similar institutions, could be cited, but the progression of the disease in old age seems to be a more general phenomenon. Rich plausibly correlated the lower resistance to tuberculosis at various periods of life with the lower resistance against other infections, and was able to cite

a certain amount of evidence from controlled laboratory observation on antibody production for the importance of innate bodily factors in resistance.

ALLERGY AND IMMUNITY

Differences have long been recognized in the character of the lesions resulting from first and superinfections. These are qualitative and quantitative and have given rise to comprehensive theories of the genesis of the disease. The whole question has acquired a newly conspicuous position because of the increasing postponement of first infection to the years of adolescence and the corresponding first contact at this important life period in the nonallergic rather than the allergic state. The facts that first infection has always taken place in the nonallergic state and that an incalculable number of allergic children have been repeatedly reinfected in their early years have been largely lost from sight in the present concern as to the resistance or susceptibility of the nonallergic and the allergic youth of the teen or early adult age.

The most widely publicized theory of the genesis of pulmonary tuberculosis in relation to the phenomenon of allergy is that of Ranke.[32] According to his conception, tuberculosis is to be divided, with relation to allergy, into three stages: (1) the primary complex, representing first infection in the nonallergic body, (2) a stage of generalization through many organs, during a period of high allergy, and finally (3) the stage of chronicity with healing of the extrapulmonary lesions and progression of the disease in the lungs, this stage being characterized by less allergy and greater general resistance. This theory has formed the basis of most treatment of the subject in Germany, but in this country has not attracted many adherents, largely because of the numerous exceptions to the second and third stages. Abroad, too, the frequent failure of correlation of stage and allergy, the common absence of any recognizable second stage and the not infrequent occurrence of generalization in the third stage have made the concept of limited use.

On the other hand, that a previous infection changes the body's reaction to subsequent infections, so that a different type of lesion results, is not questioned. Dissension starts from the commonly accepted fact that typical fibroulcerative tuberculosis, i. e., common phthisis, does not occur as a result of first infection, but only after, and commonly long after, a first infection, the lesion of which was of quite different anatomic character. It should not be overlooked that even this concept is now disputed by certain investigators who hold that the age of the patient rather than a previous infection and resultant altered immunologic response controls the character of the common pathologic process

32. Ranke, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, Julius Springer, 1928.

of adult life. Most students of the problem, however, think in terms of allergy or of increased resistance, due to the primary infection, and a dependently altered anatomic response in the case of subsequent progressive reinfection or superinfection. Some difference of opinion occurs as to whether allergy is to be credited with the alteration in anatomic response or whether a commonly concomitant but fundamentally different phenomenon called immunity is responsible. That a distinction can be achieved between the two is now no longer doubted, for typical sensitiveness to tuberculin can be removed from an infected animal by appropriate treatment, without loss of demonstrable increased resistance to fresh infection.

However, demonstrable allergy is commonly present before the development, and during the course, of chronic progressive pulmonary tuberculosis in man. The great dispute is whether allergy is the cause of the destructive disease, or whether the disease is destructive in an allergic body for reasons other than the allergy. Phrased otherwise, it is not denied that destructive disease occurs only (with occasional exceptions) in an allergic body, but it is seriously doubted that this proves allergy to be the cause of the destructiveness of the disease.

At least four important facts appear to be overlooked by those who claim that allergy predisposes to destructive disease. They are as follows:

1. Animals infected artificially in the laboratory with tubercle bacilli of low virulence are at the same time allergic and more resistant than normal animals to fresh infection with virulent tubercle bacilli. This fact has been demonstrated so many times that it is no longer disputed. Obviously this fact does not prove that allergy is responsible for the increased resistance. I have already stated that by suitable experiments an additional attribute, designated immunity, can be shown to be present in the body with allergy, but distinguishable from it. But at least there is as good correlation of allergy and resistance to destructive disease in experimental animals as there is of allergy and susceptibility to destructive disease in man.

Actually, however, in man, also, in the presence of allergy resistance is a far more common phenomenon than susceptibility to infection. Three facts may be cited to complete the list of four facts apparently overlooked by those who claim allergy predisposes to destructive disease. They will be listed as 2, 3 and 4 in conformity with the outline already commenced.

2. The lesion of first infection itself heals rather than becomes destructive in the presence of allergy. First infection occurs in a non-allergic body, and in general first infection runs a benign course. However, early in that course allergy develops. The disease does not

promptly become destructive with the development of allergy but, on the contrary, in the great majority of cases gradually becomes arrested while the allergy continues. It can be shown, to be sure, that healing occurs after allergy has passed its peak of intensity, but there is quite as good ground for saying that allergy lessens as the disease heals as for saying the disease heals because allergy lessens.

3. The life period in which the greatest increase of allergic persons occurs is the life period of greatest freedom from destructive tuberculosis. There is little active, not to mention fatal, tuberculosis in the population between the ages of 4 and 14 years, even in the most crowded centers, where infection is widespread. There are still many communities in this country where the incidence of positive reactors to tuberculin increases from 25 to 75 per cent in the age period 4 to 14 years. Yet in these communities, as elsewhere, there is little progressive tuberculosis in this period. Now it can hardly be argued that in a community where tuberculous infection is so widespread that half the population of a given age period become infected they are infected but once. On the contrary, they are presumably infected many times. The first infection sets up a small lesion, usually too small to be found by roentgen examination or other method, and the subsequent infections that must occur either do not "take" or have no more effect than the first infection. In brief, if allergy predisposed to destructive disease, a progressive increase of destructive disease in the age span 4 to 14 years should occur, but the fact is that it does not.

4. The final fact is that postmortem observation demonstrates healed tuberculosis of the reinfection type to be almost as common as healed tuberculosis of the first infection type. It will be generally admitted that if attention in the postmortem room is confined to patients dying of destructive pulmonary tuberculosis, evidence of arrested previous primary infection will be found in almost all of them. But the fact is commonly overlooked that if a similar number of bodies with healed reinfection type tuberculosis, e. g., with the common apical scars of old tuberculosis, are examined, evidence of arrested previous primary infection will be found in most of them also. This would indicate that infection is as likely to become arrested as to progress in the presence of a previous lesion. But it must not be forgotten that the number of bodies with healed tuberculosis of the reinfection type, i. e., isolated apical and other scars, is vastly larger than the number of bodies with progressive tuberculosis. Aschoff,[9] citing figures from Puhl, once stated that the majority of bodies with evidence of healed primary tuberculosis contain evidence also of reinfection tuberculosis. Half of the patients so infected, he stated, get absolutely well, and progressive disease of the lungs develops in only a small proportion of the remainder.

From such facts as these it can well be argued that first infection protects against the progression of subsequent infections. Laboratory experience bears out this argument. However, as I have stated repeatedly, the protection may be independent of the hypersensitivity concerned. I may conclude this phase of the discussion by adding that in the occasional reinfection that progresses the progression likewise may be quite independent of the allergy present. It is possible that the importance of allergy has been overemphasized by both sides.

In final analysis, whatever the role of allergy in defense, it is not decisive in determining the effect of later tuberculous infections. Either healing or progression may take place in the presence of allergy.

When, then, are the decisive factors determining the course of pulmonary tuberculosis? The balance of this paper will be devoted to a brief consideration of what may be acceptable and what may be disputed in this respect.

DECISIVE FACTORS IN THE COURSE OF PULMONARY TUBERCULOSIS

Dosage.—Few will doubt the importance of the dosage of tubercle bacilli. It must be recalled at this point that general agreement is yet to be reached as to whether chronic pulmonary tuberculosis of the reinfection type represents endogenous or exogenous reinvasion. In either event, however, the dosage of infecting bacilli must play a decisive role. If a focus of infection is present and a few bacilli escape, to lodge in uninfected tissue, multiple defensive forces of the body will hold them in check. If a huge number of bacilli escape, the various defensive forces will be overwhelmed and progressive disease will occur locally or generally. In most cases of pulmonary tuberculosis a scattering of tubercles throughout the body is found. However, generalized miliary tuberculosis, with massive infection throughout the body, is found in a few cases. Presumably the decisive factor in the two situations is the number of bacilli concerned. Other factors being equal, there is likely to be a proportionate relation between the size of the first infecting dose and the extent of subsequent endogenous spread. The greater the original dose the less likely it is that the first infection will heal, and the greater, accordingly, will be the likelihood of large rather than small doses in spread. Although the doses of endogenous reinvasion in the body are not likely ever to be measured satisfactorily, this hypothesis is sufficiently plausible not to be contested.

Likewise there is little argument that if exogenous reinvasion is the common cause of the pulmonary tuberculosis of adult life, the size of the reinfecting dose is of the utmost importance. Again, it is virtually impossible to measure the doses of bacilli that lead to spontaneously acquired tuberculosis in man, whether in primary or subsequent infection. However, the results of laboratory experience, showing that mild

infections can be overcome and that large doses will break through the defense, are so clear that few will deny that the size of the exogenous dose in man also must be decisive.

Constitutional Factors.—A few investigators, however, feel that the size of the dose concerned is not the final, decisive factor, and that the outcome will depend on the innate resistance of the body. Wallgren [32] has made a strong expression of this view in the following statement:

> The first prerequisite that pulmonary tuberculosis shall develop is a tuberculous infection. . . . The second prerequisite . . . is a disposition, and among all the constitutional and conditional factors which together constitute the concept of disposition to consumption the most significant are heredity and that the age of puberty shall have been reached. . . . In a small part of all infected persons, particularly through heredity but also through environmental conditions and other unfavorable circumstances, there is a disposition to lung tuberculosis, and of these infected persons the majority develop consumption.

Whether or not this is regarded as exaggeration, it is a fact that increasing attention is being paid to inherent or constitutional factors in relation to resistance to tuberculosis. Native resistance has always been included in discussion of factors responsible for the discrepancy in severity of tuberculosis in white persons and Negroes, but, as already indicated, the conditions of human existence are such as to make impossible an evaluation of the separate roles of environment, including dosage of bacilli and heredity. However, animal experimentation can be controlled rigidly, and the experiments of Wright and Lewis [33] and Lurie [34] show definitely that within a single animal species variation in resistance to tuberculosis is great. This holds not only for differences between pure strains of animals within the species but for heterozygous animals as well. A heterozygous pair will yield offspring of varying resistance to tuberculosis, and the variation will run true if the descendants of the low and high resistance groups, respectively, are inbred.

It is argued by many that similar facts must hold for man. The school with this view admit the importance of dosage but insist that dosage alone is not decisive. They admit that the incidence of pulmonary tuberculosis is high in families intensely exposed to tubercle bacilli and low in families without much exposure. But they stress the fact that in families with heavy exposure many members escape disease in spite of infection as frequent and presumably as great as that of those who succumb.

To illustrate the difference in point of view in simple fashion one may think of a large family with high exposure and with an ultimate total of 30 per cent contracting clinical pulmonary tuberculosis and 70 per cent

33. Wright, S., and Lewis, P. A.: Am. Natur. **55**:305, 1921.
34. Lurie, M. B.: Proc. Soc. Exper. Biol. & Med. **39**:176, 1938.

not contracting the disease. Thirty per cent is a far higher proportion than obtains in families not heavily exposed, and those stressing the decisive role of environment and dosage will point to this excessive rate as evidence of the supreme importance of dosage. The other group, however, who believe in the importance of human variability in resistance, will point to the remaining 70 per cent in the families with heavy exposure and cite their freedom from clinical disease, in spite of the exposure, as evidence of constitutional resistance. The two groups will be impressed by different sides of the same picture, but there is evidence of an increasing willingness to admit that both sides are important.

In final analysis, therefore, there is an approach to agreement that the decisive factors for progression of pulmonary tuberculosis are dosage of tubercle bacilli, whether endogenous or exogenous, and constitution. The concept of constitution in this view, however, is broad. It includes primarily heredity, but it includes also the nutritional state and other elements of body resistance that may be modified by environment.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Martha Wollstein, at one time pathologist to the Babies Hospital, New York, died September 30, at the age of 70.

W. S. Stanbury, director of laboratories, Mountain Sanatorium, Hamilton, Canada, has been appointed senior lecturer in clinical pathology at the University of Leeds, England.

George R. Murray, the discoverer of the thyroid treatment of myxedema, at one time professor of comparative pathology in Durham University, England, and later professor of medicine in Manchester, England, has died.

Louis C. Kress has been appointed director of the cancer division of the New York State Health Department. The division is charged with carrying into effect the new anticancer program provided for by recent legislative enactment. In "upstate" New York cancer is now a reportable disease.

Ernest C. Dickson, who served as assistant professor of pathology, professor of medicine and then professor of public health and preventive medicine in Stanford University School of Medicine, San Francisco, has died at the age of 58.

The following appointments have been made at Columbia University, New York: Erik J. Kraus, formerly professor of pathology in the University of Prague, visiting professor of pathology; Gregory Shwartzman, bacteriologist to the Mount Sinai Hospital, New York, clinical professor of bacteriology; Max Pinner, chief, division of pulmonary diseases, Montefiore Hospital, New York, clinical professor of medicine.

Hardy A. Kemp, professor of bacteriology and preventive medicine at Baylor University, Dallas, Texas, has become dean of the college of medicine at the University of Vermont. He is also head of the reorganized department of bacteriology, hygiene and preventive medicine.

Salmonella Center.—The International Salmonella Center has been opened under the direction of F. Kauffmann in the State Serum Institute in Copenhagen, from which immune serums and test cultures can be obtained and to which cultures can be sent for examination.

New Jersey Provides for Blood Tests in Paternity Cases.—Authority to order blood tests in cases of disputed paternity is established by the law recently adopted. The tests are to be made by duly qualified physicians, appointed by the court. This is the fourth state to adopt a law of this kind, the other states being New York, Ohio and Wisconsin.

Society News.—The sessions of the Section on Medical Sciences (N) of the meeting of the American Association for the Advancement of Science at Columbus, Ohio, Dec. 27-30, 1939, will be devoted mainly to a symposium on the blood, heart and circulation.

Fellowships for Cancer Research.—The Finney-Howell Research Foundation, Inc., announces that all applications for fellowships for next year must be filed in the office of the foundation by Jan. 1, 1940. Applications received after that date cannot be considered for 1940 awards, which will be made on March 1. Fellowships carrying an annual stipend of $2,000 are awarded for the period of one year with the possibility of renewal up to three years. When deemed wise by the board of directors, special grants of limited sums may be made to support the work carried on under a fellowship. Additional information may be obtained from the foundation, 1211 Cathedral Street, Baltimore.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Effect on Red Cells in the Rat Fetus of Gastric Juice Administered During Pregnancy. J. Stasney, G. M. Higgins and F. C. Mann, Am. J. M. Sc. **197**:690, 1939.

Concentrated samples of human and hog gastric juice were administered daily to pregnant rats during a part of the gestation period. As soon after parturition as possible, blood was obtained by cardiopuncture from the young rats born to these adults, and observations were made on the total number of red cells per cubic millimeter, the volume of packed cells per hundred cubic centimeters of blood, the greatest diameter of the red cells and the volumes of the red cells. These data were contrasted with comparable data on young rats born to mothers which received inactivated samples of gastric juice and with data on young rats born to untreated normal mothers. The following conclusions are reported: Human gastric juice, obtained after a test meal or an injection of histamine, and hog gastric juice, obtained from a fundic pouch, contain a substance which when administered to the pregnant adult rat accelerates the reduction in size and volume of the developing red blood cells of the newborn rat. This substance causes an increase in the number of red cells per cubic millimeter of fluid, a decrease in the percentage of packed red cells, a decrease in the greatest diameter of the red cells and a decrease in the volume of the red cells. These changes induced in the red cells of the newborn rat are, as a rule, proportional to the amount of gastric juice administered to the adult rat during gestation. Heating samples of gastric juice renders the substance ineffective. The macrocytosis which occurs normally in mammalian fetuses may be due to an inadequate amount of the antianemic principle, which is provided by the mother. This effect on the size and volume of red blood cells may prove to be a means of assaying the potency of antianemic principle.

From Authors' Summary.

Effect of Gonadectomy and Administration of Anterior Pituitary Extract on Cartilage and Bone of Immature Guinea Pigs. M. Silberberg and R. Silberberg, Am. J. Path. **15**:55, 1939.

In immature guinea pigs gonadectomy causes an increase in proliferation of the euhyaline cartilage in various cartilaginous tissues. In males hyperplastic growth is more accentuated, whereas in females a tendency to hypertrophy is more pronounced. The latter is especially evident within the joints, where lesions are initiated more readily than in males. In males degeneration occurs more frequently and to a greater extent than in females. Calcification and ossification of the cartilage appear balanced in females, but in males the zone of ossification shows marked disturbance. Associated with this disturbance is a tendency toward fibrosis of the bone marrow. The cause of the increase in proliferation is seen in nonspecific stimulation of the anterior lobe of the pituitary subsequent to gonadectomy. Differences in the behavior of the sexes are tentatively explained as due to differences in the inhibiting action of the gonads on the pituitary gland in the male and in the female, and also to differences in the action of gonadectomy on the thyroid gland in the two sexes. A combination of the action of an acid extract of the

anterior lobe of the pituitary of cattle and of castration leads to a summation effect which is determined by different degrees of stimulation exerted in the various tissues.

FROM AUTHORS' SUMMARY.

ON THE CAUSE OF THE ELEVATION OF SERUM PHOSPHATASE IN JAUNDICE. S. FREEMAN, Y. P. CHEN and A. C. IVY, J. Biol. Chem. **124**:79, 1938.

Serum phosphatase was determined in the following induced conditions involving the liver of the dog: (1) leptospiral infection; (2) chronic carbon tetrachloride intoxication; (3) bile fistula; (4) obstructive jaundice by ligation of the common or hepatic bile ducts; (5) partial hepatectomy. All of these with or without jaundice caused an increase of serum phosphatase—generally higher in obstructive jaundice than in hepatitis. A rise in serum phosphatase was observed to be a more sensitive indicator of hepatic injury than an elevation of serum bilirubin. The increase in serum phosphatase is not necessarily associated with jaundice.

Evidence is submitted to suggest that the phosphatase contained in bile originates in the liver and that its presence in excessive amounts in the circulation indicates leakage of phosphatase as a biliary constituent into the blood stream.

R. J. LEBOWICH.

ANTIBODY RESPONSE TO SWINE INFLUENZA. C. T. ROSENBUSCH and R. E. SHOPE, J. Exper. Med. **69**:499, 1939.

Antibodies that neutralize the virus of swine influenza became detectable in the serum of swine on the sixth or seventh day after infection. Their appearance corresponded rather closely with clinical recovery. In swine with milder filtrate disease the neutralizing antibodies did not appear until some time between the seventh and tenth days. The maximum antibody titers ranged from 1:60 to 1:160 and were attained between the fourteenth and the twenty-seventh day after infection.

FROM AUTHORS' SUMMARY.

THE ACTION OF PRONTOSIL-SOLUBLE [NEOPRONTOSIL] AND SULFANILAMIDE ON THE PHAGOCYTIC ACTIVITY OF LEUKOCYTES AND ON THE DISSOCIATION OF STREPTOCOCCI. R. TUNNICLIFF, J. Infect. Dis. **64**:59, 1939.

Prontosil soluble (now known as neoprontosil [disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonate]) in concentrations of from 1:1,000 to 1:1,000,000 and sulfanilamide in concentrations of from 1:100,000 to 1:2,000,000 in salt solution promote phagocytosis of greening and hemolytic streptococci. Both preparations appear to stimulate the activity of leukocytes but do not act as opsonin. Stabilized R cultures of greening streptococci are more phagocytosable than the stabilized S forms. Streptococci grown in 1 per cent dextrose broth containing prontosil-soluble in concentrations of from 1 to 10 per cent or sulfanilamide in concentrations of 1 to 1,000,000 show, by chain formation and granular growth, some S → R change which appears to make streptococci of the type found in pus. Both prontosil-soluble and sulfanilamide when injected subcutaneously into mice in amounts which give approximately the same blood levels of free sulfanilamide appear to stimulate the activity of the leukocytes to the same degree.

FROM AUTHOR'S SUMMARY.

HISTOLOGIC STUDY OF THE BLOOD CELLS AND BLOOD VESSEL WALLS IN ANAPHYLACTIC SHOCK IN THE CHICK EMBRYO. A. FERRIER, Ann. d'anat. path. **13**: 421, 1936.

A process resembling anaphylactic shock, discovered by Baumann, can be produced in the chick embryo during the second or third day of incubation by an application of human blood serum. The reaction depends on presence of Forssman

antigen in the embryo. The author studied such material histologically. Within five minutes after the application of the serum and before the reactions were visible grossly, he found swelling, degenerative changes and other abnormalities in the blood cells and vascular endothelium, especially well seen in the area vasculosa. The process appears to be the morphologic expression of an antigen-antibody reaction. In the embryo at this age the peripheral nervous system has not yet developed, and the reaction appears, therefore, to be entirely a humoral one, without regulation by the nervous system. PERRY J. MELNICK.

EXPERIMENTAL STUDIES OF TISSUE CALCIFICATION. R. LERICHE, A. JUNG and M. DEBAKEY, Ann. d'anat. path. **13**:551, 1936.

The authors were interested in testing out further the two factors which seem to be involved in pathologic calcification: (1) increased calcium content of the environment in which the calcifying tissue is located and (2) "dystrophy" of the tissue concerned, varying from ischemia to necrosis. For this purpose pieces of cartilage from the ears of rabbits were transplanted into the abdominal walls of the same rabbits (homologous transplants) or into the spleens of rats (heterologous transplants). After two hundred and twenty-five days the homologous transplants had calcium contents up to eight times the normal. The heterotransplants had up to forty-six times the normal calcium content. Some of both series of animals were inoculated with from 10 to 40 units of parathyroid extract daily, but the transplanted pieces of cartilage in these animals showed no difference in calcium content from those in animals not receiving the extract. PERRY J. MELNICK.

EXPERIMENTAL TUBERCULOUS MENINGITIS. ALFRED BOQUET, Ann. Inst. Pasteur **61**:479, 1938.

Studies of 41 human and 24 bovine strains of tubercle bacilli, freshly isolated and injected intrameningeally into rabbits in 0.01 to 0.001 mg. doses, indicated that the bovine types had normal virulence, the animals presenting paralysis by the third week and dying in a few days thereafter, whereas the human type, suboccipitally injected, usually caused no trouble. A few human strains produced fatal meningitis, but the interval (thirty-six to one hundred days) between inoculation and death was longer than with bovine types. Injury during inoculation upset the balance. Older strains of the bovine type were also distinctively infective. Some human strains were infective on intravenous injection but not on intrameningeal injection, and vice versa. FROM AUTHOR'S SUMMARY.

Pathologic Anatomy

BODY BUILD AND HEART SIZE. W. J. COMEAU and P. D. WHITE, Am. Heart J. **17**:616, 1939.

The heart size as determined by several orthodiascopic measurements was investigated in 20 pairs of identical twins and in 15 pairs of unrelated persons of the same sex with similar body height and weight. The data show a close correspondence of heart size in the identical twins. In the pairs of unrelated persons the similarity in the heart measurements, although less marked, is rather close, particularly when constitutional and racial differences in body structure which are not brought out by height and weight alone are considered. The conclusion is reached that in normal persons heart size is dependent principally on body build and that genetic, racial and environmental factors are usually important chiefly as they affect body structure. The combination of height and weight, although the best index of body build that is known, is not completely satisfactory. It is hoped that anthrometric studies may produce a more reliable index for expressing body build and thereby offer a more satisfactory measurement to correlate with heart size. FROM AUTHORS' SUMMARY.

THE POSTMORTEM WEIGHT OF THE "NORMAL" HUMAN SPLEEN AT DIFFERENT AGES. E. B. KRUMBHAAR and S. W. LIPPINCOTT, Am. J. M. Sc. **197**:344, 1939.

The ratio of spleen weight to body weight was found to be highest at birth and to fall steadily while the spleen was attaining its maximum absolute weight. From the age of 26 years on, the ratio fell slightly except for an apparent rise between 50 and 65 years.

In general, the spleens of males were heavier than those of females, and those of white people were heavier than those of Negroes. As the difference between the spleen weights of white people and Negroes was greater than that between the spleen weights of males and females, sex appears to be a less important factor than color. In none of the aforementioned categories were differences between mean spleen weights of individual groups to be attributed to corresponding differences in mean body weights. The average weight for all the adult spleens (16 years or over) was 150.7 Gm.; for spleens between the ages of 16 and 70, 154 Gm.; for all 4,000 spleens, 140.7 Gm. The weight of the apparently normal human spleen fluctuates within extremely wide limits. Weights as low as 100 Gm. and as high as 250 Gm. were not infrequently recorded, while even such weights as 50 and 400 Gm. were occasionally given for what appeared to be normal spleens.

Analysis of the causes of death in the "disease group" showed little beyond the prevalence of acute respiratory disease in the groups between 16 and 25 years of age and of arteriosclerosis in the older age groups. The former of these may well be a factor in the spleen weight peak in the two young groups, and the latter, a factor in the loss of spleen weight in older life. Analysis of the histologic appearances in the "disease group" showed that the lesions diagnosed in about 75 per cent of the spleens would tend to cause an increase in weight. Only 2.5 per cent of the spleens were listed as atrophic. FROM AUTHORS' SUMMARY.

FIBROSIS OF THE LUNGS. G. T. HEBERT, Tubercle **20**:145, 1939.

Since fibrosis of the lungs has several etiologic factors and takes a different form with each, it is advisable to specify the predominant or essential type, whether peribronchial, interstitial or perifocal, when speaking of fibrosis. The chief diseases which cause fibrosis are each associated particularly with one type —chronic bronchitis with peribronchial fibrosis, bronchopneumonia with interstitial, and tuberculosis and silicosis with perifocal. In certain forms of tuberculosis and silicosis the interstitial type accompanies, follows or masks the perifocal type. The history of the case is always a valuable guide to the diagnosis of fibrosis. The physical examination gives good evidence of the interstitial types but poor evidence of the perifocal and peribronchial types. The role of the roentgenogram is to show (1) positive shadows wholly or partially due to perifocal fibrosis and (2) evidence of contraction in interstitial fibrosis. When an incorrect diagnosis of fibrosis is made from the roentgenogram, it is usually the case that the wrong interpretation has been placed on positive shadows cast by inflammatory changes. The history and clinical condition of the patient will not only suggest whether it is likely that inflammatory changes are present, for which due allowance must be made in the reading of the shadows, but will also give an indication of the type of fibrosis that may be expected. H. J. CORPER.

ACUTE MENINGOCOCCIC INFLAMMATION OF THE ADRENALS (WATERHOUSE-FRIDERICHSEN SYNDROME). E. RUTISHAUSER and H. BARBEY, Ann. d'anat. path. **13**:143, 1936.

The article presents a review of the literature on adrenal hemorrhage. A case is presented in which the background was meningococcic septicemia. There were complex clinical and anatomic findings, including multiple areas of myositis in the pharyngeal muscles, tongue and diaphragm; acute myocarditis; hyperemia of the

islands of Langerhans and of the mucosa of the trachea and bronchi; thrombosis and necrosis of the glomerular tufts of the kidney; diffuse hepatitis and thrombosis of the central veins; necrosis of the pulmonary elastic tissue, and other changes, as well as other septic findings. There was also bilateral adrenal hemorrhage with thrombosis of the veins. In a somewhat philosophic discussion of the physiologic mechanisms involved, an attempt is made to separate the endocrine from the septic factors.

PERRY J. MELNICK.

SCLEROTIC AND SO-CALLED INTERSTITIAL FORMS OF PULMONARY TUBERCULOSIS. F. BEZANCON and J. DELARUE, Ann. d'anat. path. **13**:241, 1936.

On the basis of a study of the results of 650 autopsies in cases of pulmonary tuberculosis, the authors present an analysis of the various fibrotic forms, with special reference to the histologic character of the early lesion. This they find to be interstitial "reticular" pneumonitis. This interstitial process is apparently common to all the various forms of fibroid tuberculosis. At first there is a thickening of the alveolar walls by capillary dilatation and cellular infiltration; the cells are soon predominantly histiocytes and reticulum cells, and the latter are soon transformed into fibroblasts, which lay down interweaving bundles of collagen fibers surrounding dilated blood vessels. From this point various types of changes take place, depending on the type of fibrosis which supervenes. A brief but adequate description of these various forms of fibroid tuberculosis is included.

PERRY J. MELNICK.

THE ENDOCRINE GLANDS AND THE BRAIN IN OLD AGE. L. EINARSON and H. OKKELS, Ann. d'anat. path. **13**:557, 1936.

Histologic studies of the organs in advanced age, especially the endocrine glands, constitute a difficult and rather thankless type of research. It is difficult to separate the changes due to age alone from the results of the many intercurrent infections and traumas, small and large, sustained by the subject with the passing years. It is especially difficult to separate the changes due to arteriosclerosis, which is not necessarily a function of age. Autopsies on persons of advanced age without arteriosclerosis should therefore be of much interest, but are rare. Einarson and Okkels report such an autopsy on a 93 year old woman who died of pneumonia following fracture. The findings, which resembled closely those in a similar case reported from the Pasteur Institute, were chiefly those of atrophy and involution. In both, the only important observations among the endocrine glands were large adenomas of the adrenal cortices, which the authors would like to correlate with a possible influence on cholesterol metabolism and the absence of arteriosclerosis. The essential change in the brain in each instance was "lipoid degeneration," with large accumulations of lipophages, especially in the cornu ammonis and the olivary nuclei. The possible influence of the nervous system on the aging process is discussed.

PERRY J. MELNICK.

HERNIA OF THE ABDOMINAL VISCERA THROUGH THE NORMAL ORIFICES OF THE DIAPHRAGM. R. GARRAND and P. BASTIEN, Ann. d'anat. path. **13**:603, 1936.

The article consists chiefly of a review of the literature on diaphragmatic hernia, with special emphasis on hernia through the normal orifices, i. e., those for the esophagus, inferior vena cava, aorta, sympathetic nerves, splanchnic nerves and others. The anatomy, genesis, clinical features, roentgen diagnosis and treatment of the disease are discussed. There are 2 illustrative case reports, and a large bibliography is appended.

PERRY J. MELNICK.

CONCUSSION OF THE BRAIN. W. NEUGEBAUER, Frankfurt. Ztschr. f. Path. **51**:210, 1938.

After a review of the pertinent literature, Neugebauer describes 50 cases of fatal injuries of the skull with frequent cerebral hemorrhages. Of 14 cases in which there were clinical signs of concussion of the brain, microscopic hemorrhages were observed in the mesencephalon or rhombencephalon in 13. Hemorrhages were found in 31 other cases, but the latter were incompletely observed clinically. In 5 cases in which there were no symptoms of concussion, the author did not find these changes. Small hemorrhages might be repaired, while larger ones cause permanent disturbances. The variety of the symptoms may be explained by the different locations of the hemorrhages. Regarding the origin of the latter, the author points out that, owing to increased pressure in the fourth ventricle and in the sylvian aqueduct, laceration of adjacent areas of the brain tissue occurs. The deep hemorrhages are due to diapedesis following stasis. The author recommends substitution of the term "concussion of the brain" with a more specific term such as "traumatic lesion of the cortex, medulla, basal ganglions, mesencephalon and rhombencephalon."

OTTO SAPHIR.

Pathologic Chemistry and Physics

DETERMINATION OF CHOLESTEROL AND CHOLESTEROL ESTERS IN TISSUES BY THE SCHOENHEIMER-SPERRY METHOD. S. STURGES and A. KNUDSON, J. Biol. Chem. **126**:543, 1938.

The method of Schoenheimer and Sperry for the estimation of cholesterol and its esters in blood has been adapted for the determination of these factors in tissues. The new microcolorimetric method checks with the macrogravimetric method. Owing to interference by digitonin, the colorimetric determination is carried out by means of a filter of a pore diameter between 610 and 630 microns, the region of maximum absorption for digitonin.

R. J. LEBOWICH.

CHEMICAL NATURE OF FACTORS PRODUCING THE SHWARTZMAN PHENOMENON. D. GLICK and W. ANTOPOL, J. Infect. Dis. **64**:22, 1939.

Extractability of both preparative and reactive Shwartzman factors was found to be independent of p_H between 8.65 and 4. Below a p_H of 4 lessened preparative potency was observed in extracts tested with winter rabbits, while provocative potency could not be demonstrated. Spring rabbits were found to be more sensitive, but the preparative potency still was greater than the provocative. Protein-free carbohydrate fractions of Bacillus proteus possessed considerable provocative but no preparative power. Shiga polysaccharide gave irregular results, but a protein-free Shiga preparation of Morgan containing fatty and polypeptide materials in addition to polysaccharide was shown to have both factors. Glycogen and kerasin were found to have no ability to prepare cutaneous sites, though they could elicit reactions when used intravenously in rabbits prepared with active B. proteus extracts. The quantities of these two substances necessary to produce reactions were much greater than those required when purified B proteus preparations were employed.

FROM AUTHORS' SUMMARY.

PORPHYRINS IN BIOLOGY AND PATHOLOGY. J. THOMAS, Bull. Soc. chim. biol. **20**:1058, 1938.

The characteristic green color of chloroma of the suberiosteum, kidneys, brain and other tissues is due to protoporphyrin, which can be readily detected by its red fluorescence under the Wood light.

R. J. LEBOWICH.

Microbiology and Parasitology

EFFECT OF 1,2,5,6-DIBENZANTHRACENE ON GROWTH OF YEAST. E. S. COOK SR., M. J. HART and R. A. JOLY, Am. J. Cancer **35**:543, 1939.

The effect of 1,2,5,6-dibenzanthracene on the proliferation and respiration of yeast can be stimulative or inhibitory, depending on concentration. In the range of concentration most effective for the promotion of growth a reversal of the respirant effect, from stimulation to inhibition, takes place.

FROM AUTHORS' SUMMARY.

ETIOLOGY OF ULCERATIVE COLITIS. R. LIUM and J. E. PORTER, Am. J. Path. **15**:73, 1939.

In 6 cases of ulcerative colitis it was demonstrated at autopsy that the severest lesions were in the rectum, overlying the tenial bands. This distribution of lesions over the most powerful muscles of the colon may well be due to the fact that hypermotility and spasm of the colonic muscles cause the disease. Supportive evidence for this interpretation is the fact that early lesions of ulcerative colitis have been produced in the colons of dogs by hypermotility and spasm of the muscles alone.

FROM AUTHORS' SUMMARY.

TUBERCULOSIS OF THE TONSILS: ITS INCIDENCE AND ORIGIN. E. R. LONG, M. V. SEIBERT and L. M. GONZALEZ, Arch. Int. Med. **63**:609, 1939.

Two thousand unselected pairs of tonsils from routine tonsillectomies were sectioned and examined microscopically for tuberculosis. One thousand pairs came from various Indian reservations, known to be communities of high tuberculosis morbidity; 600 from Puerto Rico, a region with much tuberculosis but of lower tuberculosis morbidity than the Indian reservations, and 400 from Philadelphia, a community of low tuberculosis morbidity in comparison with the other two. Tuberculosis was found in 81 pairs of tonsils; including 6.5 per cent of the tonsils from the Indian reservations, 2.5 per cent of those from Puerto Rico and 0.25 per cent of those from Philadelphia.

All stages of regression of tonsillar tuberculosis from active fibroplastic disease to scars indistinguishable from scars of other origin were seen in the series. The relatively massive tuberculosis of the tonsils in cases of pulmonary tuberculosis, its tendency to be bilateral and its chronicity all point to repeated infection of these organs in the course of the pulmonary disease. Since all studies of tuberculosis of the tonsils show that tonsillar involvement occurs in a large proportion of cases of pulmonary tuberculosis, and since small tubercles tend to regress, there is reason to believe that at some time or other in the course of the disease the great majority of patients with progressive pulmonary tuberculosis, if not all of them, have tuberculosis of the tonsils.

FROM AUTHORS' SUMMARY.

A STUDY OF RICKETTSIAE GROWN ON AGAR TISSUE CULTURES. H. ZINSSER, F. FITZPATRICK and H. WEI, J. Exper. Med. **69**:179, 1939.

Guinea pigs treated with formaldehydized or phenol-killed rickettsias from agar tissue cultures are either completely immunized or rendered so much more resistant than normal animals that only a late and very slight reaction results from subsequent inoculation with large doses of passing virus. By this method, unlike any of the others, the available amount of organisms becomes practically unlimited.

LYMPHOCYTIC CHORIOMENINGITIS — ITS DIAGNOSIS IN MAN. M. HOWARD, J. Infect. Dis. **64**:66, 1939.

The virus of benign lymphocytic choriomeningitis was isolated from the spinal fluid of a patient early in the course (sixth and seventh days) of the infection,

when the cellular response in the spinal fluid was at its height. Abnormalities were slow in disappearing from the spinal fluid. Neutralizing antibodies in the patient's serum were demonstrated in low titer late in convalescence when mice as the test animals and the virus isolated from the patient were used. No sample of the patient's serum protected against Rivers' W. E. strain of the virus in guinea pigs. Reinoculation experiments and the protection afforded by serum from Rivers' patient W. E. gave proof of the immunologic identity of this strain with others already described. The virus isolated lost its virulence for guinea pigs during constant passage in mice. A discussion of the problem of diagnosing clinical infections of this type is presented.

FROM AUTHOR'S SUMMARY.

ABSORPTION OF BACTERIOPHAGE BY BLOOD CELLS AND BACTERIA. M. A. CONGRESS, J. Infect. Dis. **64**:83, 1939.

Bacteriophages active against staphylococci, streptococci, colon bacilli and typhoid bacilli were not absorbed by washed human red corpuscles and leukocytes. Staphylococcus and streptococcus phages were partially absorbed by homologous susceptible strains but not by phage-resistant strains. Colon and typhoid bacillus phages were not absorbed by either resistant or susceptible homologous strains. Partial absorption of colon bacillus phage was observed with susceptible dysentery strains.

FROM AUTHOR'S SUMMARY.

EFFECT OF GASTRIC MUCIN ON PATHOGENICITY. C. G. ANDERSON and R. K. OAG, Brit. J. Exper. Path. **20**:25, 1939.

Anderson and Oag throw light on the mechanism by which mucin increases the virulence of certain bacteria. The subject of virulence is still very obscure; there is involved an interplay of invasive and toxic properties on the part of the micro-organism and of various modes of resistance by the host. The activity of mucin is shown to be due to the protein moiety, the carbohydrate fraction being inactive, although other carbohydrates, such as agar and polysaccharides derived from the diphtheria bacillus, have the same effect as mucin.

BACTERIAL ASSOCIATION IN AMEBIASIS. R. DESCHIENS, Ann. Inst. Pasteur **61**:5, 1938.

Experimental studies with cultures and with animals and epidemiologic and clinical investigations lead Deschiens to believe that the intestinal bacterial flora is either a major or a minor factor in amebiasis. The colon bacillus, typhoid bacillus and paratyphoid A and B bacilli were the principal organisms used experimentally.

FROM AUTHOR'S RÉSUMÉ.

VIRULENCE OF HUMAN TUBERCLE BACILLI FOR THE RABBIT. L. NÈGRE and J. BRETEY, Ann. Inst. Pasteur **61**:109, 1938.

Guinea pigs were treated with acetone extract of tubercle bacilli and then inoculated with the blood of tuberculous guinea pigs (human strain). Two strains of tubercle bacilli isolated from these animals exhibited marked pathogenicity for rabbits. One lost this power to infect rabbits after four years on glycerin-potato medium, although it still infected guinea pigs. On the other hand, certain strains, freshly isolated on egg medium, infected rabbits readily on intravenous injection of 0.01 mg. When originally cultured, the growth was hemispheric, shiny, firm and adherent. These characteristics were later lost, without loss of particular virulence for the rabbit. The cultures studied retained all other characteristics of the human type.

FROM AUTHORS' SUMMARY.

VIRUS OF VENEREAL LYMPHOGRANULOMA. W. GAVRILOF and FESTER, Arch. Inst. Pasteur de Tunis **28**:1, 1939.

The Nauck strain of virus, received in its twenty-eighth passage in mice, was studied in vivo and in vitro. When this strain was inoculated in the brains of mice, elementary bodies, stained by Giemsa's stain, appeared in the spleen and liver, diminishing in number up to seven days in mice that survived. Death in three to six days was characteristic. The virus was maintained successfully in Maitland's medium, on the chorioallantoic membrane of the chick embryo and in tissue cultures on the cornea, but not on the cornea in vivo. Following the development of a group of elementary bodies in cultures, an acidophilic mass was formed in the protoplasm similar to those formed in other virus infections. In dogs both general and local reactions were irregularly observed after one day. The serum of infected dogs did not have protective properties. Lymph nodes contained elementary bodies which, even when the dogs showed no reaction, still infected other animals.

M. S. MARSHALL.

A CASE OF MEASLES IN WHICH GIANT CELLS WERE OBSERVED IN THE RESPIRATORY TRACT. M. MASUGI and G. MINAMI, Beitr. z. path. Anat. u. z. allg. Path. **101**:283, 1938.

Masugi and Minami report their pathologic observations on a 9 month old girl who died of secondary bronchopneumonia four days after the appearance of a measles exanthem. The buccal, faucial, pharyngeal, bronchial and esophageal mucous membranes revealed many multinucleated giant cells containing inclusion bodies. None were noted in the tonsils, appendix, mesenteric lymph nodes and spleen. In morphologic structure the giant cells, which are regarded as having their origin in local epithelial cells, corresponded completely to those described by Warthin and Finkeldey in tonsils removed during the prodromal stage of measles. They contained many crowded, hyperchromatic nuclei. Regressive changes in both the nuclei and the cytoplasm may be present. The inclusion bodies are usually multiple and are situated close to the nuclei. The inclusion bodies vary considerably in size and are round in contour in their typical form. They are counterstained a homogeneous intense red in hematoxylin and eosin preparations. Measles is regarded as a disease caused by an epitheliotropic virus.

R. J. LEBOWICH.

Immunology

IMMUNIZATION AND SENSITIZATION WITH STREPTOCOCCUS. D. M. ANGEVINE, J. Exper. Med. **69**:211, 1939.

When a relatively avirulent strain of hemolytic streptococci was injected into the skin of rabbits a considerable amount of cutaneous sensitivity to streptococcus filtrate developed, and there was scant demonstrable immunity. When the same strain of streptococci was made highly virulent by repeated passages through rabbits, little sensitization and considerable immunity were produced. Rabbits given injections of a virulent culture of this strain of hemolytic streptococci produced agglutinins and precipitins earlier and in larger amounts than animals given injections of the avirulent form of the same organism. An increase in the virulence of hemolytic streptococci enhances the ability to protect against local infection and increases antibody formation but diminishes the development of sensitization. Avirulent and virulent strains of this micro-organism have similar relations.

FROM AUTHOR'S SUMMARY.

TYPE-SPECIFIC SUBSTANCE FROM GROUP A HEMOLYTIC STREPTOCOCCI. G. K. HIRST and R. C. LANCEFIELD, J. Exper. Med. **69**:425, 1939.

A substance extracted from hemolytic streptococci of group A is described, which induces active immunity in mice, and in rabbits gives rise to precipitins and

to protective antibodies which are passively transferable to mice. The active immunity in mice is principally type specific, but some degree of immunity that is not type specific also develops. The passively transferable protective antibodies are type specific with only a slight suggestion of the presence of antibodies that are not type specific. In the precipitin test the rabbit immune serum gives both type-specific and nontype-specific reactions, which have not been fully analyzed serologically. Substances contained in the extract absorb the protective antibodies from the serum of rabbits immunized with whole hemolytic streptococci. The most satisfactory method of extraction so far developed is fully described. Chemical tests on the material are consistent with the presence of protein and nucleic acid. The type-specific M substance, prepared as previously described, was compared in some of its antigenic properties with the aforementioned substance. It was found capable of inducing active immunity in mice and of absorbing protective antibody from antibacterial immune serum in a manner qualitatively similar to that noted with the preparations made by the newer methods.

FROM AUTHORS' SUMMARY.

SOLUBLE MALARIAL ANTIGEN. M. D. EATON, J. Exper. Med. **69**:517, 1939.

In the serum of monkeys infected with Plasmodium knowlesi there occurs a soluble malarial antigen which fixes complement with immune serum. The amount of antigen in the serum is related to the parasite count during the acute phase of the infection. The antigen is not excreted in the urine. Serum containing this antigen when injected into normal monkeys intravenously stimulates production of specific complement-fixing antibodies which react with antigens extracted from parasitized cells as well as with the antigen present in serum obtained during the acute phase of infection. Monkeys immunized with the serum antigen apparently possess little or no immunity to infection. The soluble malarial antigen is labile to acids and alkalis, is not destroyed by a temperature of 56 C. and is precipitated, for the most part, in the albumin fraction of the serum by ammonium sulfate.

FROM AUTHOR'S SUMMARY.

PREGNANCY AND IMMUNITY TO ST. LOUIS ENCEPHALITIS. H. L. HODES, J. Exper. Med. **69**:533, 1939.

Virgin and pregnant Swiss mice are equally susceptible to intracerebrally injected St. Louis encephalitis virus. Following subcutaneous vaccination with the St. Louis virus, the great majority of virgin Swiss mice become immune to 10,000 M. L. D. of the virus intracerebrally injected. The majority of mice vaccinated during pregnancy do not become immune to even as little as 500 M. L. D. of the virus intracerebrally injected. The depression of the ability to acquire immunity against the virus is most marked when the vaccination is carried out late in pregnancy, but it is demonstrable when the mice are vaccinated early in the period of gestation or during the first two weeks post partum. Seven weeks post partum the response to vaccination is more nearly like that of virgin mice. Pregnancy not only interferes with the acquisition of immunity, but it diminishes previously established immunity. Offspring of the mice vaccinated during pregnancy are not immune to 100 M. L. D. of virus.

FROM AUTHOR'S SUMMARY.

THE O RESISTANCE OF VI STRAINS. A. W. POT, J. Infect. Dis. **64**:110, 1939.

Experiments are described and discussed which show that Vi strains are able to combine with O agglutinins.

FROM AUTHOR'S SUMMARY.

CELLULAR REACTIONS IN THE SKIN, LUNGS AND INTESTINE AFTER INFECTION WITH NIPPOSTRONGYLUS MURIS. W. H. TALIAFERRO and M. P. SARLES, J. Infect. Dis. **64**:157, 1939.

These data in conjunction with those previously reported by the authors indicate that immunity against Nippostrongylus muris is largely dependent on humoral factors with secondary cellular cooperation and is manifested as follows: Antibodies (precipitins and possibly other humoral factors) immobilize, form precipitates in and around, stunt and sometimes kill the worms. They also localize the irritating excretions and secretions of the worm and bring about more intense inflammatory responses. Basically, immunity is identical in the skin, lungs and intestine; it is only apparently different in the intestine in that the immobilized worms are expelled directly from the body instead of being encapsulated in nodules. Immunity develops during the second week of the initial infection and is therefore manifested first in the intestine. After one or several light reinfections immunity is largely limited to the intestine. After several heavier reinfections it is manifested not only in the intestine but in the lungs. Finally after heavy reinfections it is manifested in all three sites. This successive involvement of the various organs is probably related to the length of sojourn and the physiologic activities of the worms during the course of infection and to the antibody titer of the host.

FROM AUTHORS' SUMMARY.

TOXIC EXTRACTS FROM STREPTOCOCCI. L. COTONI and J. POCHON, Ann. Inst. Pasteur **61**:45, 1938.

Streptococci were grown in Weld's medium, from which they were separated and shaken with inactivated animal serum. The resultant product killed mice and rabbits when injected intravenously. Hemolytic streptococci of human origin were most productive. There was not a proportional relation between toxigenicity, hemolytic activity and pathogenicity for mice. The properties are similar in many respects to those of streptococcus hemolysin, but with some strains hemolytic activity occurs without toxicity.

M. S. MARSHALL.

Tumors

GLOMUS TUMOR. S. BLINDER, Am. Heart J. **17**:238, 1939.

Glomus tumors are benign arterial neuromyomatous lesions of the glomus, a structure normally present in man and other warm-blooded mammals. The history of a purple-bluish or reddish area of discoloration, commonly located under the nail bed but sometimes found elsewhere, which has been present for a long time and is associated with characteristic paroxysms of local pain, makes the clinical diagnosis readily apparent. A case of glomus tumor is presented. Examination eighteen months subsequent to complete surgical removal showed apparently permanent recovery. This result confirms those obtained in all cases previously reported. Once the diagnosis has been established, immediate surgical removal is advised.

FROM AUTHOR'S SUMMARY.

TUMORS OF THE HEART AND PERICARDIUM. R. W. SCOTT and C. F. GARVIN, Am. Heart J. **17**:431, 1939.

In a series of 11,100 consecutive postmortem examinations made at the Cleveland City Hospital during the past twenty years there were 1,082 in which malignant disease was disclosed. In 118 of the cases of cancer i. e., in 10.9 per cent, the heart, including the pericardium was involved by metastasis. Carcinoma of the bronchus and carcinoma of the breast invaded the heart and pericardium most often, accounting for 48 per cent of the cases in this series. The development of congestive cardiac failure in a patient with malignant disease, without other apparent cause, was the most important clinical symptom pointing to cardiac metastasis.

FROM AUTHORS' SUMMARY.

TRANSITIONAL GLIOMAS. G. LEVIN, Am. J. Cancer **35**:22, 1939.

Nine cases of a glial tumor for which the name "transitional glioma" has been suggested (Globus) have been studied. The course is moderately rapid. More often the patient is in the fourth or fifth decade of life. The mechanism of growth and the gross anatomic features are similar to those of any other incompletely differentiated glioma. The tumor is composed of ill defined areas, among which there is a difference in the grade of cellular differentiation. The tumor probably consists of foci of less differentiated glia interspersed among forms more generally mature. It thus represents an unconsummated transition of the undifferentiated and therefore more malignant forms of gliogenous tumor into the more differentiated and essentially benign types.

FROM AUTHOR'S SUMMARY.

ASSOCIATION OF SILICOSIS AND CARCINOMA OF THE LUNG. M. O. KLOTZ, Am. J. Cancer **35**:38, 1939.

An analysis of the statistics of the department of pathology and bacteriology of the University of Toronto shows an incidence of pulmonary cancer of 8 per cent among 50 silicotic patients as compared with an incidence of 1.17 per cent among 4,500 unselected patients.

URINE EXTRACTIVES IN CANCER. H. SOBOTKA and E. BLOCH, Am. J. Cancer **35**: 50, 1939.

The lipoid extracts of 2,100 liters of pooled urine from persons with cancer were fractionated and compared with analogous fractions from controls. No positive chemical or biologic evidence for the presence of carcinogenic hydrocarbons was obtained, though small amounts of dibenzanthracene and phenanthrene added to 100 liters of normal urine were easily recovered. Except for an increase in the cholesterol fraction no significant deviations were observed.

FROM AUTHORS' SUMMARY.

TUMOR PRODUCTION IN MICE WITH ULTRAVIOLET IRRADIATION. H. P. RUSCH and C. A. BAUMANN, Am. J. Cancer **35**:55, 1939.

When albino mice were irradiated for thirty to sixty minutes daily, tumor of the ear developed in 62 to 83 per cent within three and a half to nine months. Tumors developed more rapidly in mice irradiated daily for long periods than in those irradiated for short periods. No difference in the rate of development or in the total incidence of tumors was observed between two strains of albino mice. A smaller percentage of tumors developed in black mice than in albinos, and the time required was greater. Tumors developed more rapidly in mice in rotating cages than in mice in stationary ones. Various gradations of papilloma, epithelioma and spindle cell sarcoma were produced. The altered epithelial cells varied from typical epidermal cells of the cell nest to those closely resembling spindle cells. Excellent material for the study of the early changes in the pathogenesis of tumors is thus available. Ultraviolet radiation is a good carcinogenic agent for experimental studies. It is nontoxic in the ordinary sense; the dose is easily controlled, so that the period of induction of the tumors can be varied at will, and the development of the tumors can be readily followed. Albino mice are ideal animals for such studies.

FROM AUTHORS' SUMMARY.

NEUTRALIZATION OF THE ACTIVE AGENT OF FILTERABLE FOWL TUMORS. R. J. LUDFORD, Am. J. Cancer **35**:63, 1939.

In tissue culture flasks containing a plasma clot composed of fowl plasma and embryo extract there is present occasionally a neutralizing substance capable of inactivating a filtrate of Fujinami sarcoma. This neutralizing substance may occur both in the presence and in the absence of cultures of buffy coat from normal and

resistant birds. It has been found in Tyrode sclution, embryo extract and filtrates of Fujinami sarcoma and of Gye's dibenzanthracene sarcoma after these various materials have been incubated for several days with plasma clots. In the preparation of cultures, the employment of embryo extract prepared from the eggs of birds immune to the Fujinami virus does not result in the presence of the neutralizing substance in the fluid mediums of the cultures. Tyrode solution when incubated with plasma clots has been found to have the same neutralizing property. Some of the clots were prepared with the plasma of a bird the serum of which contained antibodies, and others were prepared with plasma from another bird without demonstrable antibodies in its serum. The neutralizing substance thus appears to be related to some property of certain kinds of plasma. It might be some product resulting from the action of enzymes in the embryo extract on some constituent of certain kinds of plasma or, alternately, the experimental results could be explained on the assumption that antibodies to the virus of the Fujinami tumor are present in the blood of some "normal" birds and that these may be present in the plasma although not detectable by neutralization tests with the serum. In working with tumor viruses in tissue cultures it is desirable to bear in mind the possibility of a neutralizing substance being present in the culture mediums.

FROM AUTHOR'S SUMMARY.

DES LIGNERIS FOWL SARCOMA. C. R. AMIES, J. G. CARR and W. J. PURDY, Am. J. Cancer **35**:72, 1939.

A study has been made of the des Ligneris sarcoma—a filtrable avian tumor which originated in a fowl inoculated with normal chicken fibroblasts which had been cultivated in vitro with dibenzanthracene. In its structure and behavior this tumor closely resembles the Fujinami sarcoma. This view is considerably strengthened by the fact that cell free extracts give rise to progressive tumors in ducklings. Ducks in which a des Ligneris tumor has developed and subsequently regressed are immune to the tumor agent of the Fujinami sarcoma. Various immunologic experiments indicating that the des Ligneris tumor is related to Rous sarcoma no. 1 are compatible with this belief.

FROM AUTHORS' SUMMARY.

COMPARATIVE ACTIVITY OF SOME CARCINOGENIC HYDROCARBONS. J. M. TWORT and C. C. TWORT, Am. J. Cancer **35**:80, 1939.

Dissolved in chloroform, 3,4-benzpyrene was about five times as carcinogenic as 1,2,5,6-dibenzanthracene. Methylcholanthrene was about twice as carcinogenic as benzpyrene. The crystalline picrates of a pinene synthetic tar made at 850 C. were about as carcinogenic as dibenzanthracene. The frequency of hyaline degeneration and enlargement of the spleen was related to the carcinogenicity of the agent applied. The frequency of spindle cell epithelioma was also, apparently, related to the carcinogenic activity of the agent. Cells rendered irreversibly cancerous by benzpyrene were not retarded by hydrous wool fat from developing into a tumor. Cells rendered abnormal by a few applications of benzpyrene quickly passed into the irreversibly cancerous phase when stimulated by oleic acid. Liquid petrolatum, hydrous wool fat and some other agents apparently had no such action.

FROM AUTHORS' SUMMARY.

EXTRA-CHROMOSOMAL THEORY OF BREAST CANCER IN MICE. J. J. BITTNER, Am. J. Cancer **35**:90, 1939.

The maternal influence in the genesis of the mammary tumors observed in hybrid mice produced by crosses of high and low tumor mice may be explained by a "breast cancer–producing influence" transmitted in the milk of potentially high tumor mothers. There is some evidence that a sufficient amount may be transferred by the inoculation of a graft of normal tissue to initiate the development of mammary cancer in some cases. The nature of this "influence"—hormone, chemical or virus—has not been determined.

FROM AUTHOR'S SUMMARY.

ASPIRATION FOR REMOVAL OF BIOPSY MATERIAL FROM THE LIVER. E. BARON, Arch. Int. Med. **63**:276, 1939.

Forty-eight hepatic aspirations have been performed on 35 patients. There have been no serious complications due to the employment of this procedure. The subcostal is preferred to the intercostal route, in order to obviate the danger of hemorrhage. In 1 case a small piece of colonic mucosa was recovered, owing to penetration of the colon, but there were no untoward results. Hepatic aspiration has been of great value in the diagnosis of metastatic carcinoma and in the differential diagnosis of jaundice. It is also of value in the diagnosis of less common diseases, such as congenital cystic disease, cavernous hemangioma and schistosomiasis. It has been found of little value in the diagnosis of cirrhosis.

Since this paper was submitted for publication there has been 1 case in which death was directly attributable to the procedure. The patient was a man with extensive metastatic carcinoma of the liver. Death was due to a small rent in the surface, measuring about 1 cm., which permitted an exsanguinating hemorrhage.

FROM AUTHOR'S SUMMARY.

NEUROGENIC TUMORS ARISING FROM THE SACRUM. A. W. ADSON, F. P. MOERSCH and J. W. KERNOHAN, Arch. Neurol. & Psychiat. **41**:535, 1939.

Neurogenic tumors—chordoma, ependymoma, ganglioneuroma, neurofibroma and teratoma—may originate, according to the authors, not only in the cerebrospinal axis or in the peripheral nervous system but also in the sacrum. Chordoma, which was observed in 19 cases, originated in the sacral bone itself or in its hollow. The cells of this tumor, which are usually vacuolated, contained mucus, glycogen and what the authors call paraglycogen. The latter substance gives a positive reaction for glycogen after fixation in a solution of formaldehyde. The contents of other vacuoles could not be determined.

Ependymoma, which was observed in 7 cases, appeared in 4 instances as myxopapillary, for the stroma tended to undergo myxomatous degeneration. A ganglioneuroma observed in a child originated from the hollow of the sacrum and almost filled the pelvis. Neurofibroma, of which there were 3 cases, originated in 2 cases in the hollow of the sacrum and in 1 case posterior to the sacrum. In the latter case it was associated with spina bifida occulta. Teratoma, observed in 1 case, was situated in the hollow of the sacrum and in the retroperitoneal tissue. It consisted mainly of adult brain tissue, in which it was possible to identify cerebral and cerebellar tissue.

G. B. HASSIN.

CARCINOMA OF THE UTERINE CERVICAL CANAL. R. LEROUX and J. L. MILLOT, Ann. d'anat. path. **13**:65, 1936.

In 84 carcinomas of the uterine cervical canal which were encountered in a series of 1,511 carcinomas of the uterus between 1921 and 1934, the authors distinguish the following histologic types: adenocarcinoma (of several varieties); squamous cell carcinoma; undifferentiated carcinoma; mixed forms. Brief discussions of the histogenesis, stromal reaction, radiosensitivity and clinical course are included. Metaplasia of the squamous and glandular epithelium is considered an important factor in the histogenesis. Because of the long duration of the local precancerous changes, the authors consider carcinoma of the cervical canal to have a relatively favorable prognosis.

PERRY J. MELNICK.

EOSINOPHILIA IN MALIGNANT TUMORS. J. L. RIOPELLE, Ann. d'anat. path. **13**: 467, 1936.

Eosinophilia in the course of malignant tumors is rare. The author reports the clinical and autopsy observations in a case in which the eosinophilic cells varied from 24 to 78 per cent, this eosinophilia occurring in the course of extensive metastases of an adenocarcinoma. The metastases were chiefly to the lymph

nodes; the primary site of the adenocarcinoma could not be identified with certainty. About the metastatic cancers there were extensive infiltrations of eosinophilic leukocytes. The eosinophilia was of splenic and myelogenous origin; it appears in this case, therefore, to have been solely a defensive reaction against the tumor cells and not stimulated by the products of tumor degeneration or similar factors.

PERRY J. MELNICK.

ISOLATED LYMPHOGRANULOMATOSIS OF THE SMALL INTESTINE. L. EFSKIND, Acta chir. Scandinav. **80**:317, 1938.

Efskind describes granulomatosis of the small intestine in 2 men, 56 and 60 years old. A tabulated review is submitted of 13 cases collected from the literature, in most of which the condition occurred in males. The symptoms are indefinite, so that in none of the cases was a diagnosis made during life. The main symptom is diarrhea, which rapidly leads to a marantic condition; then fatal perforative peritonitis begins. The period of survival after the onset has averaged nine months. The process starts primarily in the mucosa and submucosa, probably unilocularly, and spreads to the mesenteric glands. The infection is assumed to be enterogenous, so that the intestinal process with the infiltration of the tributary glands forms the primary complex, an assumption which quite definitely contradicts the belief that lymphogranulomatosis is a systemic disease with multiple primary lymphatic foci. Enterogenous infection in lymphogranulomatosis may be more frequent than is assumed.

FROM AUTHOR'S SUMMARY.

Society Transactions

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

MORTON MCCUTCHEON, *President*

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NATURAL AND ACQUIRED IMMUNITY TO STAPHYLOCOCCIC TOXIN IN MONKEYS. CHARLES WEISS, Mount Zion Hospital and University of California, San Francisco.

The blood serum antistaphylolysin (alpha) of 65 normal monkeys (Macacus irus and Macacus mulatta) varied from 0 to 25 units. Their response to parenteral injection of staphylotoxin depended in each instance on the original titer and the route of immunization. Animals with high initial titers (10 units or more per cubic centimeter) acquired antibodies more rapidly and to a much higher level than those with low values.

No definite relationship was established between the serum titers and the skin reactivity to staphylotoxin. As in the case of diphtheria, there was no fixed level at which the reactions of individual animals passed from the negative to the positive group, or vice versa. Skin reactivity in actively or passively immunized animals was likewise inconstant. In the latter the skin reactions remained negative when the antitoxin curves had returned to approximately their original levels.

In actively or passively immunized animals there was no correlation between survival or death after intrabronchial injection of staphylotoxin and the intensity of the skin reactions or the serum titer.

Natural and acquired immunity against the dermonecrotic or lethal effects of staphylotoxin depend not only on the amount of circulating antistaphylolysin but on additional factors probably comprised under the heading of cellular or tissue immunity. A study of beta and gamma antilysins and of toxin prepared in synthetic mediums is under way.

A TEST OF THE LATTICE HYPOTHESIS WITH A BIVALENT HAPTEN. SANFORD B. HOOKER and WILLIAM C. BOYD, Boston University School of Medicine, Boston.

The lattice hypothesis of aggregative reactions necessarily assumes both antibody and antigen to be multivalent. "With simple haptene molecules, which have only one determinant group, neither building up of aggregates nor deformation of antibody molecules can, in general, occur." "If only two determinant groups are attached to one molecule, an aggregate of unlimited size . . . can be built up." We have prepared a hapten (paraparadicarboxydiphenyl) with two presumably identical and fairly well separated determinant groups in whose pattern the carboxyl should be the important central point. Tested with an antiserum to a paraaminobenzoic protein compound, it did not precipitate, although its inhibiting power was, as expected, greater than that of paraaminobenzoic acid itself. Despite the presumably high dissociability of hapten from antibody, if the antibody is highly multivalent, this result is not in accord with what the lattice hypothesis would predict.

Incidentally, the results of some roughly quantitative measurements of the inhibitive power of a number of related substances are presented.

PASSAGE OF PROTEINS FROM THE VASCULAR SYSTEM INTO JOINTS AND CERTAIN OTHER BODY CAVITIES. GRANVILLE A. BENNETT and MORRIS F. SHAFFER, Harvard Medical School, Boston.

Previous studies have demonstrated that egg and horse serum proteins injected intra-articularly are removed from joints solely by lymphatics, whereas certain drugs of small molecular dimensions in aqueous solution are removed from joints chiefly by the blood capillaries. The present experiments were undertaken to study comparatively the transference of certain foreign proteins from the blood stream into synovial fluid, aqueous humor, spinal fluid and urine.

Rabbits were used, and crystalline egg albumin or horse serum protein fractions were injected intravenously. By employing the precipitin test with specific antiserums as a means for their detection, these proteins could be demonstrated to have passed regularly, within a short period, from the blood stream into the joints. They also appeared in the aqueous humor, but in lower concentration. In the majority of experiments, no foreign protein was detected in the spinal fluid; when present its concentration was never more than minimal. Egg albumin was passed rapidly via the kidney, whereas horse serum proteins were detected only occasionally, in low concentration, in the urine.

These experiments, demonstrating that the synovial membrane is more permeable to the foreign proteins employed than are the membranes separating the aqueous humor and the spinal fluid from the vascular system, seemingly explain (1) the higher homologous protein concentration of normal synovial fluid as compared with spinal fluid and aqueous humor, and (2) the very high protein concentration found in long-standing joint effusions. They also suggest certain studies on the hypersensitivity of articular tissue and have a bearing on the possible treatment of infections of joints with specific antiserums.

COMBINED THERAPY FOR PNEUMOCOCCIC INFECTIONS OF THE RAT: RABBIT ANTIPNEUMOCOCCUS SERUM AND SULFAPYRIDINE (2-[PARAAMINOBENZENESULFONAMIDO]-PYRIDINE). H. M. POWELL and W. A. JAMIESON, Eli Lilly and Company, Indianapolis.

Prolonged intensive immunization of rabbits with pneumococci leads to the development of antiserum containing both type-specific and broadly acting antibodies. The latter are stronger when selected cultures are used as antigen, and have likely been dealt with previously by Tillett, Day, Harley, Bailey, Dubos and others.

The use of such broadly acting antiserum, with antibodies demonstrable for six of the more common types of pneumococci, and sulfapyridine as a combined therapy has been assayed in a comparative way in rat protection tests. In general, 0.001 cc. of antiserum, a dose of itself effective mainly against the smallest doses of culture, becomes as effective as 0.1 cc. of antiserum against maximum doses of test culture when used in conjunction with partially effective sulfapyridine medication. The combined treatment appears of enhanced effectiveness when compared with either antiserum therapy or chemotherapy alone.

INCREASED RESISTANCE TO VACCINIA DUE TO TREATMENT WITH ESTROGEN. DOUGLAS H. SPRUNT and SARA MCDEARMAN, Duke University, Durham, N. C.

In a recent publication we reported that estrogen when injected into castrated rabbits decreased the spread of india ink and also increased the resistance of rabbits to infection with vaccinia. We pointed out that other workers had noted similar phenomena in association with various endocrine states.

Since the publication of this paper, Parker has described a method by which it can be shown that transmission of vaccinia is dependent on the presence of one virus particle in the inoculum. Parker's method was thought to be excellent for the study of quantitative variations in the resistance of the host to infection.

This paper is the report of a number of experiments done according to Parker's method. The results show clearly that the estrogen in castrates and pseudopregnancy in normal females increase the resistance to vaccinal infection by about 30 per cent. The possible causes for this increase in resistance are discussed.

SPUTUM STUDIES IN PNEUMONIA: THE EFFECT OF SULFANILAMIDE. ARTHUR W. FRISCH, Wayne University, Detroit.

The effect of sulfanilamide in 50 patients who had been proved roentgenographically to have pneumonia was followed from specimens of rusty sputum obtained during the acute phases of the disease. The number of free capsulated pneumococci per oil immersion field was determined from smears treated with Wright's stain for blood.

A rapid decrease in the number of extracellular pneumococci occurred in twenty-four hours. No change in the size of the capsule and no increase in phagocytosis has as yet been detected. The organisms, however, tended to assume bizarre shapes, stained poorly and became somewhat pyknotic. In some cases the preliminary reduction was followed by subsequent reappearance of the pneumococci in the sputum on the fourth to the fifth day of therapy. The possible relation of the development of active immunity, as indicated by spontaneous clumping of the extracellular pneumococci, to the phenomena described is discussed.

EFFECTS OF SULFANILAMIDE, PHENOTHIAZINE AND THIONOL IN EXPERIMENTAL TRICHINOSIS. JAMES B. MCNAUGHT, RODNEY R. BEARD and FLOYD DE EDS, Stanford University, San Francisco.

The following procedures were used in evaluating the efficacy of various therapeutic agents against trichinosis. White rats infected with equal numbers of encysted trichinella larvae were segregated into groups of four each in cages designed to permit determination of the amount of food consumed. One group on the standard rat diet served as controls. Three other groups were kept on the same diet plus the following drugs in the concentrations indicated: sulfanilamide, 1.6 per cent; phenothiazine, 0.25 per cent, and thionol, 0.25 per cent. Six weeks after infection all rats were put to death, their carcasses digested and counts made of the total number of trichinella larvae in the muscles of each.

The animals on sulfanilamide received an average daily dose of 0.96 Gm. per kilogram of rat, with a total group intake of 37.7 Gm. They made no gain in weight. There was a 55 per cent reduction in the number of larvae recovered as compared with the control group. The group on phenothiazine received an average daily dose of 0.14 Gm. per kilogram of rat, or a total intake of 3.8 Gm. of the drug. This group gained 18 per cent over its original weight and showed a 74 per cent reduction in the number of larvae recovered. The group on thionol received an average daily dose of 0.13 Gm. per kilogram of rat, or a total intake of 4.2 Gm. The group gained only 4 per cent over the original weight and showed a 45 per cent reduction in the number of larvae recovered.

We conclude from our preliminary results (1) that sulfanilamide and thionol are inferior to phenothiazine in controlling experimental trichinosis and (2) that phenothiazine shows promise of being a useful drug in the treatment of trichinosis and warrants further experimentation which is now in progress.

EFFECTS OF SOJOURN IN AN EXPERIMENTALLY INFECTED ROOM ON THE MOUSE VIRULENCE OF A STRAIN OF GROUP B BETA HEMOLYTIC STREPTOCOCCUS. LEON BUCHBINDER, MATHILDE SOLOWEY and MORRIS SOLOTOROVSKY, Columbia University College of Physicians and Surgeons, New York.

A series of studies are being carried out on the longevity of streptococci sprayed into an experimental room as well as on the effects of that environment on the properties of the recovered organisms.

This report is concerned with the effect of survival in the room on the mouse-killing properties of a strain of group B beta hemolytic streptococcus, the 090 strain. This strain is normally highly virulent for mice. We have found that one organism (chain) is fatal in almost all instances. Cultures were recovered from the room daily for about two weeks, and their virulence for mice was compared by titration with subcultures of the original unsprayed culture. It was found (1) that in no instance did any recovered culture appear to have its virulence lessened when injected in the 1×10^{-6} dilution (100 to 400 organisms), (2) that in the greatest majority of instances the virulence of the recovered culture was unaltered in the 1×10^{-7} and 1×10^{-8} dilutions, (3) and that in a small percentage of the recovered cultures there was some apparent loss of virulence in the 1×10^{-7} and 1×10^{-8} dilutions.

PHOTO-OXIDATION OF ANTIGENS AND ANTIBODIES. H. SMETANA and D. SHEMIN, Columbia University College of Physicians and Surgeons, New York.

Quantitative studies of the precipitin reaction of normal and of photo-oxidized antigen and antiserum showed that the precipitin reaction was markedly altered by photo-oxidation of either antigen or antiserum. Comparative precipitin curves of normal and photo-oxidized antigen demonstrated that the greater the photo-oxidation the more antigen nitrogen was needed to reach the peak of the curve but that the height of the peak was the same.

Chemical analyses of photo-oxidized antigen indicated that the tryptophan was progressively destroyed; in the early stages of photo-oxidation there seemed to be a direct relation between the total nitrogen precipitated and the amount of tryptophan present in the antigen.

Precipitin curves of photo-oxidized antiserums showed that the greater the photo-oxidation the less antigen was needed to reach the peak of the curve, in each instance, while the height of the peak was progressively lowered.

The protein fractions of antiserum were isolated by electrophoresis, and quantitative analyses of their precipitating properties were made; the influence of photo-oxidation on the component carrying the precipitating property was then studied.

Physicochemical changes of antigen and antibody fractions of serum occurring during photo-oxidation were demonstrated by employing electrophoretic and ultracentrifugal methods.

PREPARATION OF PURIFIED ANTIPNEUMOCOCCUS ANTIBODIES. ANTHONY M. MOOS and FRANK B. ABLONDI, Lederle Laboratories, Inc., Pearl River, N. Y.

A systematic investigation of the reactions between serum proteins and naphthylamine and naphthal monosulfonic and disulfonic acids was made. In the case of immune rabbit serum, the solubility of the immune globulin derivatives in a given naphthalene sulfonic acid solution is a function of the p_H, structure, concentration and dissociation constant of the naphthalene sulfonic acid.

By the use of the appropriate naphthalene sulfonic acid, it was possible to prepare, with a quantitative recovery, antipneumococcus antibody solutions containing up to 98 per cent specifically precipitable nitrogen.

Antipneumococcus antibody solutions prepared according to this method are insoluble in the absence of electrolytes and show other similarities in behavior to horse antipneumococcus antibody.

COMBINING POWER AND PROTECTIVE VALUE OF ANTIPNEUMOCOCCUS RABBIT ANTIBODY. A. J. WEIL, Lederle Laboratories, Inc., Pearl River, N. Y.

Antipneumococcus rabbit serums treated with substituted naphthylamine sulfonic acids may undergo a change in their biologic qualities which finds expression (1) in a gradual lowering of the number of (mouse) protective units per milligram of antibody and (2) a gradual loss of the power of fixing complement.

These experiments indicate that a determination of combining power as measured by any precipitative method with carbohydrate as antigen is not always equivalent to a determination of protective properties: Combining power is not the only determinant of biologic (protective) value.

ABSORPTION OF RADIOACTIVE IRON. P. F. HAHN, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Single feedings of the radioactive isotope of iron were given and the appearance of this metal in the plasma and erythrocytes studied. The radioactive iron is demonstrable in the plasma in an hour and reaches a maximum value there in or about the sixth hour. The major part is found in that fraction of the plasma not precipitated by trichloroacetic acid. This may indicate that the plasma carrier is nonprotein. Some of the iron appears in the erythrocytes within a few hours after feeding and is for the most part in protein combination.

EXCRETION OF RADIOACTIVE IRON IN DOGS. ROBERT A. HETTIG and W. F. BALE, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Radioactive iron has enabled us to study the excretion of iron. In normal dogs and dogs with bile fistulas the elimination in the urine and feces as well as bile was determined following administration of ferrous gluconate by vein. Except for a temporary spilling over effect during the several days immediately following the injection, the amount found in the urine is negligible. The fecal excretion of iron is fairly high for a few days but in subsequent determinations approaches a relatively constant daily value representing about 0.1 per cent of the amount given. The biliary iron comprises only a small fraction of that excreted by the gastrointestinal tract.

OCCURRENCE OF SPONTANEOUS EXOPHTHALMOS IN ADULT GUINEA PIGS. S. H. ROSEN and D. MARINE, Montefiore Hospital, New York.

For several years we have noted the occurrence of chronic progressive exophthalmos in many adult guinea pigs of our breeding colony. This exophthalmos frequently advances to a much more marked degree than we have ever obtained with anterior pituitary extract in immature guinea pigs. It is seen only in adults, while that due to anterior pituitary extract is difficult to produce in adults. It resembles the latter in that it is rarely symmetric and in that cervical sympathectomy abolishes it. It differs in that it occurs in adults in thyroids that grossly and histologically are normal. The diet has remained fairly constant and consists of whole oats, alfalfa hay and lettuce, given daily.

A CHRONIC CECAL DISEASE OF LABORATORY RATS. HAROLD L. STEWART and BENJAMIN F. JONES, United States Public Health Service, Harvard Medical School, Boston.

The frequent occurrence in rats of a characteristic spontaneous disease involving the cecum has been observed. The condition may be described as an ulcerative cecitis associated with enlargement of the adjacent lymph nodes and with peritoneal adhesions. A striking feature of the disease is the occurrence of lymph stasis and cystic enlargement of the lymph nodes, chiefly of those in the mesentery; a chronic progressive fibrosis of the ulcerated cecum accompanies the condition. The disease was first encountered in an inbred colony of rats in Boston, and it has since been found in two colonies of pure strain albino rats in Washington, D. C. Although the incidence varies from 10 to 80 per cent, the mortality in young and middle-aged rats is not strikingly high. In the affected rat a mass develops in the lower part of the abdomen, and there is usually diarrhea alternating with bloody stools, which later subsides. In some animals the abdominal enlargement

increases to such an extent that the picture of an emaciated animal with a greatly distended abdomen results. Death is sometimes due to acute diffuse peritonitis or to massive intestinal hemorrhage originating in the ulcerated cecum.

EXPERIMENTAL PROOF OF THE OBSTRUCTIVE ORIGIN OF APPENDICITIS IN MAN. OWEN H. WANGENSTEEN and CLARENCE DENNIS, University of Minnesota, Minneapolis.

The cause of appendicitis is still a matter of debate. Diet and miscellaneous factors, such as latitude, longitude and habits of life, are alleged to be important in the genesis of appendicitis. Aschoff and his followers insist that appendicitis is a specific bacterial disease. Fitz and others, who helped to construct the pathologic concept of appendicitis, stressed the significance of factors in the origins of the disease.

Observations made on appendicostomies in man suggest that the vermiform appendix secretes fluid. In obstructed appendicostomies in man an opportunity has been afforded to study the secretion. These observations have established definitely a secretory capacity of the appendix. Secretion pressures approaching the systolic level of blood pressure have been observed, and the histologic picture of acute diffuse appendicitis attends temporary obstruction of all exteriorized appendixes whenever the secretion of fluid causes a sustained rise of intraluminal pressure.

Similar observations have been made on the cecal appendages of a large variety of animals. Only the rabbit and the chimpanzee other than man possess an appendage that secretes fluid.

Our interpretation of the bearing of these findings on currently held pathologic and clinical concepts are delineated briefly in this paper.

EXPERIMENTAL HYPOPLASTIC ANEMIA IN THE PIGEON AND ITS UTILIZATION AS A BASIS FOR THE BIOLOGIC ASSAY OF SPECIFIC HEMOCYTOPOIETIC STIMULI. CHARLES A. DOAN, CARL V. MOORE and B. C. HOUGHTON, Ohio State University, Columbus.

Preliminary biopsies of bone marrow were made during a base line period of observation, including total white cell and total red cell counts, estimations of hemoglobin and supravital differential white cell counts. Certain presumably stimulatory substances, including vitamin B_6, iron adenylate, nucleic acid, liver extract, yellow bone marrow, certain amino acids, dextrose and casein, were given, each as a supplement to the regular diet for a two week period. A second biopsy of marrow was made, and then the regular diet was discontinued and only the specific material in each instance given.

The weight curves of the animals, together with the peripheral blood findings, were taken daily and contrasted with those for control animals. Under control conditions, coincidentally with a gradual loss in weight on restriction of the diet, the pigeon shows gradually progressive hypoplasia of the marrow.

The specific hemopoietic properties of the substances tested were thus sharply delineated during the course of the experiment, the studies of the peripheral blood and of the terminal bone marrow being the basis for the final interpretations.

STUDIES ON CHEMOTAXIS: THE NATURE OF SUBSTANCES ATTRACTING OR REPELLING THE SLIME MOLD. DALE REX COMAN, University of Pennsylvania, Philadelphia.

The mechanism of chemotaxis in leukocytes, as well as the nature of the substances that excite the reaction, is not definitely known. This is due largely to technical difficulties that interfere with studying the effect on leukocytes of pure chemicals in solution. Therefore it seemed desirable to make such studies on material less vulnerable and more regular in its reactions than leukocytes. The slime mold, Physarum polycephalum, has been found admirably suitable. This

organism, a myxomycete, is a naked mass of protoplasm which resembles in behavior an enormous leukocyte and shows remarkably constant positive and negative chemotactic reactions. Since it attains a length of several centimeters, it may be studied with the naked eye, or minute fragments may be cut off from the mass and observed with the microscope. Such fragments remain mobile and in appearance are quite like macrophages.

The first series of experiments dealt with the action of two factors generally considered as playing a predominant part in chemotaxis of leukocytes, i. e., hydrogen ions and substances strongly active at the surface. It was found that the organism was invariably repelled by hydrochloric acid and sodium hydroxide in adequate concentrations, and that this effect was due to the hydrogen and hydroxyl ions, and not to either the chlorine or the sodium ions. An acid with strong surface activity (acetic acid) was used in several concentrations, and here, too, only negative responses were obtained.

In contrast to these negative effects, positive chemotaxis was produced by dextrose. However, another sugar, saccharose, gave indifferent results. Two pure proteins, insulin and crystallized egg albumin, produced no response.

It is concluded that, viewed as a general reaction of protoplasm, chemotaxis does not depend chiefly on either the hydrogen ion or the surface activity of a substance but is a more complex and highly selective reaction.

MECHANISM OF LEUKOCYTOSIS WITH INFLAMMATION. VALY MENKIN, Harvard Medical School, Boston.

The writer has demonstrated the presence of a crystalline nitrogenous substance (termed leukotaxine) in inflammatory exudates capable of inducing a prompt increase in capillary permeability and leukocytic migration. Further observations, with the technical assistance of F. Ogden and I. Lapouse, indicate that the diapedesis of polymorphonuclears into an inflamed area is evidently not referable to the mechanism that is responsible for the leukocytosis frequently encountered with inflammation. Leukotaxine injected into the circulating blood fails to induce a rise in the number of white cells.

The leukocytosis is evidently not of neurogenic origin. Denervation of a limb of a dog, performed by Dr. Luco, subsequently followed by a severe burn, failed to prevent the development of leukocytosis. The available evidences indicate that the phenomenon is probably due in large part to a chemical factor. If a sample of either whole or cell-free exudate, obtained from a dog with sterile inflammation and leukocytosis, is injected into the blood stream of a normal dog, it induces within one to three hours an appreciable increase in the white cell count, ranging from about 50 to 100 per cent. On the other hand, blood serum, sterile broth, histamine, adenosin and leukotaxine fail to induce any such increase. The rise induced by the exudate is well above the normal fluctuations in white cell counts. The factor is thermolabile. Heating the exudate for several hours at 60 C. destroys the potency of the material. The factor seems to be essentially nondialyzable. Further studies are in progress in an endeavor to identify this leukocytosis-promoting factor liberated in areas of inflammation.

STREPTOCOCCIC PRECIPITINOGEN IN THE SERUM OF HUMAN BEINGS AND MONKEYS DURING THE ACUTE STAGE OF POLIOMYELITIS. EDWARD C. ROSENOW, Mayo Foundation, Rochester, Minn.

The methods used for the isolation of the streptococci, the preparation of antiserums and the performance of precipitation tests are discussed. The results obtained with poliomyelitis antistreptococcic serum, with the serum of patients who had acute poliomyelitis in different epidemics and with the serum of monkeys when normal and after development of symptoms of acute poliomyelitis following inoculation of different strains of poliomyelitis virus are reported.

EFFECT OF HEAT ON A HOMOLOGOUS MATERIAL FROM THE BROWN-PEARCE TUMOR. ALBERT E. CASEY and VINCENT MORAGUES-GONZALES, Louisiana State University Medical Center, New Orleans.

In three experiments comprising 49 rabbits and supported by a large collateral series the crude emulsion of a material from the Brown-Pearce tumor demonstrated previously to alter the transplantability and malignancy of this tumor was shown to be somewhat inactivated when heated to 52 C. and completely inactivated when heated to 56 C. for one hour.

NATURE OF IMMUNITY TO TRICHOMONAS FOETUS INFECTION IN RABBITS. H. J. BYRNE and P. M. NELSON, University of Wisconsin, Madison.

Andrews and co-workers have shown that cows are resistant to reinfection with Trichomonas foetus after spontaneous recovery. It appeared worth while to study the nature of this immunity.

Experiments disclosed that intravaginal injections of the flagellates into normal female rabbits resulted in infections in 84 per cent, the average infection lasting twenty-three days. Following spontaneous recovery, attempts to reinfect these rabbits resulted in a marked decrease in both the percentage infected and the duration of infection. Coincidentally with the acquisition of this resistance, some of the animals showed low agglutinin titers; others did not. Moreover, animals with much higher agglutinin titers, resulting from intravenous injections of live trichomonads, were as susceptible to infection as normal, untreated rabbits.

These experiments demonstrate that an active immunity to T. foetus infection develops in rabbits, and that this immunity is independent of the agglutinin content of the blood. Apparently, the resistance to infection by this protozoan is local.

SODIUM DIPHENYL HYDANTOINATE: PHARMACOLOGIC AND HISTOPATHOLOGIC STUDIES. O. M. GRUHZIT, Research Laboratories, Parke, Davis and Company, Detroit.

Sodium diphenyl hydantoinate is a derivative of hydantoin which was shown by Putnam and Merritt to have an anticonvulsant action when used in the treatment of patients with epileptic seizures in doses of 5 to 10 mg. per kilogram. It is a white powder with a bitter, pungent taste. It is soluble in water and has a strongly alkaline reaction; its p_H is about 11.5. With weak acids it forms poorly soluble acid diphenyl hydantoin. Its toxicity varies considerably with different types of animals. It is least toxic to albino rats, the maximum tolerated dose (M.T.D.) being around 2,200 mg. per kilogram when given orally. Other animals, such as mice and pigeons, tolerate only about one fifth of the rat's dose. Rabbits tolerate well a dose of 900 mg. per kilogram. Dogs receiving daily doses of 22, 45, 65 and 110 mg. per kilogram for three to six months have retained or gained weight and have borne and nursed young without showing physical or neurologic disturbances. The hematologic state of animals under prolonged treatment with the drug has remained unchanged. The cell counts and the hemoglobin and hematocrit values have remained at normal levels. During the first two months under the administration of the drug the leukocytes showed a tendency toward hydropic degeneration. In later periods of therapy an increase of eosinophils was a constant occurrence. The physical state of the individual red cell, i. e., the size, volume, weight and hemoglobin content, remained within the normal limits of the pretreatment period. The chemical constituents of the whole blood, plasma and cells showed no changes in mineral, nitrogen or lipid content which could be differentiated from those in the normal control animals.

It requires oral administration of large doses of sodium diphenyl hydantoinate to cause visible symptoms of intoxication. In albino rats a dose of 1,000 mg. per kilogram causes mild symptoms of incoordination and spasticity and 1,500 mg. per kilogram causes prostration. The animal becomes rigid, with legs outstretched, head retracted and the body in a state of rigor. The sensation of pain and the

ocular reflexes remain unabolished. In pigeons the spastic state simulates the polyneuritis of vitamin B deficiency, which is not changed by administration of large doses of vitamin B_1.

The course of the disease in guinea pigs on a scurvy diet was not modified by the administration of sodium diphenyl hydantoinate in daily doses of 50 mg. per kilogram. Normal guinea pigs did not show any symptoms of vitamin C deficiency under prolonged treatment with it. The drug has no effect on the utilization of vitamins B_1 and C.

The drug is quite toxic when administered by the intravenous route, the minimum lethal dose (M.L.D.) being 160 mg. per kilogram for the rat and 90 mg. per kilogram for the dog. A dose of 10 mg. per kilogram causes excitement, incoordination and considerable gastrointestinal disturbance.

Oral administration of large doses may cause death in a few hours to several days. An acute death is accompanied by respiratory and cardiovascular paralysis resulting in venous stasis with multiple hemorrhages in the lungs, liver, brain and other organs. No histologic changes were present in tissues of animals receiving the drug daily for six months in doses ten times (100 mg. per kilogram) those used in clinical treatment of convulsive seizures. Sodium diphenyl hydantoinate administered by mouth appears to be well tolerated by animals.

EFFECT OF VARIOUS ENDOCRINE PRINCIPLES ON THE EXPLANTED EMBRYONAL HEART MUSCLE. E. VON HAAM and L. DAVIS, Ohio State University, Columbus.

This paper represents one of the experiments designed to study the possible pathologic effects of endocrine principles on normal cells. The effect of some of the important endocrine preparations in various dilutions is studied on the viability, growth and beat of explanted embryonal heart muscle. Careful elimination of other biologic factors and strict standardization of the experiment permit a comparison of the effects of the various substances used. The possibility of using this method in the bioassay of minimal doses of endocrine products is discussed.

HETEROLOGOUS TRANSPLANTATION OF RABBIT TUMORS. HARRY S. N. GREENE, Rockefeller Institute for Medical Research, Princeton, N. J.

The ease with which the initial transplantation of a number of spontaneous rabbit tumors was effected when the anterior chamber of the eye was used as the site of inoculation, in contrast to the complete failure of attempts to transfer the tumor by testicular and other routes, suggested that this method might be used successfully for heterologous transplantation.

The tumors employed in the experiments were spontaneous mammary and uterine growths which had been carried through a number of homologous generations by serial transfer in anterior chambers. Transfer of fragments of the tumors to the anterior chambers of guinea pigs, goats, sheep, hens and hogs resulted in takes in all instances, and the growths obtained in guinea pigs and in hogs have been maintained by serial transplantation. The characteristics of growth and the eventual fate of the tumors in the alien species have been investigated.

SUSTAINED HYPERLIPEMIA OF DIETARY ORIGIN. JESSE L. BOLLMAN and EUNICE V. FLOCK, Mayo Clinic, Rochester, Minn.

The neutral fat, cholesterol and phospholipid content of the blood of dogs twenty-four hours after feeding were determined over the course of six to fifty weeks. Variations in the fat, protein and carbohydrate contents of isocaloric diets indicated that the levels of these substances in the blood varied with the meat content of the diet but were independent of the fat and carbohydrate content. The addition of cholesterol to the diet did not alter the cholesterol content of the blood. The addition of phospholipids to the diet definitely increased the phospholipid, cholesterol and neutral fat in the blood. The extent of the increase varied

with different animals but was greatest in those receiving 10 Gm. of lecithin daily, somewhat less with 5 Gm. and still less when 2.5 Gm. of lecithin was fed. The addition of choline, in amount equivalent to 10 Gm. of lecithin, elevated these constituents of the blood, but to the extent expected from 2.5 Gm. of lecithin. These variations of the lipoid content of the blood do not appear to alter the lipoid content of the liver. The lipoid content of the liver may be changed without altering the lipoid content of the blood.

Other factors influence the lipoid of the blood as is indicated by the high values found in thyroidectomized dogs. Preliminary experiments also indicate that the lipoid level of rat blood is not influenced by diets which are effective in the dog.

STABILITY OF ASCORBIC ACID IN BLOOD. LOUIS D. GREENBERG and JAMES F. RINEHART, University of California Medical School, San Francisco.

Considerable controversy exists with respect to the stability of ascorbic acid in blood, which has thrown some doubt on the reliability of data based on determinations of the content of this vitamin in blood. In connection with extensive studies of the reduced ascorbic acid in plasma in health and in various diseases we have studied factors influencing the stability of ascorbic acid in blood. Data are presented which support the following conclusions: Whole blood kept at refrigerator temperatures does not lose an appreciable amount of its ascorbic acid in two to three hours and can be expected to give reliable analytic values within this period after withdrawal. There is no evidence to indicate that cyanide added to blood protects the vitamin from oxidation. Potassium cyanide itself decolorizes 2,6 dichlorophenolindophenol, probably by virtue of the ferrocyanide present as an impurity. In the collection and handling of blood for ascorbic acid analyses hemolysis must be avoided, since the release of hemoglobin from erythrocytes produces a loss or destruction of vitamin C that is dependent on the amount of hemolysis. This loss is not prevented by cyanide.

Methods employed in our laboratory for the determination of the ascorbic acid in blood plasma are briefly presented.

ADRENAL CORTEX AND HYPOGLYCEMIA. T. F. ZUCKER and B. N. BERG, Columbia University College of Physicians and Surgeons, New York.

Both the medulla and the cortex of the adrenal are concerned in blood sugar shifts. Cannon showed the relation between medullary function and the increase in blood sugar which occurs in cats that have been stimulated emotionally. Zucker and Berg found that animals with inactivated adrenals recovered spontaneously after insulin shock. The recovery was attributed to cortical activity.

Previous methods of adrenal inactivation, such as medullectomy, section of the splanchnic nerve or adrenalectomy, not only suppressed medullary adrenal secretion but impaired cortical function by direct injury to or interference with the nerve supply.

In order to study separately the functions of the cortex and medulla it is important to exclude one without injuring the other. This can be accomplished by means of bilateral ligation of the lumboadrenal veins. When the venous return from the medulla is blocked, epinephrine is excluded from the general circulation, while the cortex remains intact through its own independent blood supply (Flint, Elman and Rothman, Cannon).

Our experiments were performed on cats with successful bilateral ligation of the lumboadrenal veins which prevented emotional hyperglycemia (Cannon). In such animals a suitable dose of insulin did not produce shock or excessive hypoglycemia. The same dose caused no symptoms in normal animals but in medullectomized, denervated or adrenalectomized cats it produced shock and lowered the blood sugar excessively. Apparently, the change in the response to insulin which follows adrenal inactivation is due to interference with cortical function.

EXPERIMENTAL INFECTION OF MICE WITH GONOCOCCUS. C. PHILLIP MILLER and WALTER D. HAWK, University of Chicago, Chicago.

The method of infecting mice with organisms of low virulence by means of mucin, which proved highly satisfactory for meningococci, was regarded as a failure in its original purpose, which was the establishment of gonococcic infection in mice, because injections of about a million micro-organisms were required. That number of gonococci, which are very toxic, seems too great to constitute the initiation of a genuine infection. Several workers have differed with us on this point and have reported experimental gonococcic infections in mice with inoculums of this magnitude.

The present communication is a preliminary report of an attempt to enhance the virulence of gonococci for mice through rapid and persistent animal passage by intraperitoneal inoculation. Thus far the virulence of two strains has been raised sufficiently to enable an inoculum of about 100 gonococci to initiate fatal infection.

The essential point in the method seems to be the use of young cultures of blood obtained from mice dying of infection. The cultures are made by spreading two or three drops of heart blood over the surface of an agar slant, which is kept horizontal during incubation to prevent the blood from running down to the end of the tube. After twenty to twenty-two hours the growth is washed off and titrated by tenfold dilution in 5 per cent mucin (granular mucin supplied by the Wilson Laboratory, Chicago), and 1 cc. portions are injected intraperitoneally into the next batch of mice.

At the start of each series, which was begun with a freshly isolated strain of gonococci, several million micro-organisms were required to produce a lethal infection, and with several strains this number never fell below a million. In the case of two strains, however, after a few passages, the minimum lethal dose began to fall and continued to do so until about 100 gonococci—sometimes fewer—sufficed to kill. A third strain gives promise of attaining that level but has not yet reached it. Any break in the continuity of the routine, whether occasioned by holidays, illness, a poor lot of medium, contamination or other misfortune, which necessitated repeated subculture, resulted in loss of virulence. We have not yet learned how to maintain virulence during cultivation on artificial mediums.

DISTRIBUTION OF A GLYCOLIPOIDAL ANTIGEN AMONG THE NEISSERIAE. ALDEN K. BOOR and C. PHILLIP MILLER, University of Chicago, Chicago.

Several years ago we reported the study of carbohydrate from gonococci and meningococci, obtained by treating the lysed organisms with acetic acid to remove proteins and then precipitating with alcohol. This carbohydrate was free from fat and protein, was nontoxic and did not stimulate antibody formation when injected into the experimental animal. It gave a positive precipitin reaction with antiserum for the whole organism or for protein ("nucleoprotein") prepared therefrom.

Boivin and collaborators obtained a fat-carbohydrate compound from some strains of paratyphoid bacilli, from colon bacilli, from Salmonella aertrycke and others by trichloroacetic acid extraction. This product appeared to be the essential antigen derived from the somatic portion of the cell. It was toxic and specific. Raistrick and Topley obtained the same or a similar substance from aertrycke organisms by alcohol treatment of a tryptic digest. These results were rather recently confirmed by Maccolini in Italy.

For our study of the gonococcus and meningococcus, the organisms were grown on an egg digest-agar medium, usually for forty-eight hours, washed off with saline solution and centrifuged. Each gram of packed moist organisms was suspended in water to make 5 cc., then 5 cc. of half-normal trichloroacetic acid was added and thoroughly mixed. After three hours in the refrigerator the

mixture was centrifuged sufficiently to remove the precipitate, including the cellular debris, and the supernatant filtered through rather fine filter paper.

The presence of the glycolipoidal compound was indicated by opalescence of the solution. Ether extracted the fatty material after boiling with half-normal hydrochloric acid, although not before this hydrolysis. The glycolipoidal compound before hydrolysis, as well as the carbohydrate left after ether extraction of the hydrolysate, gave a strong precipitin test against antiserum for the whole organism. Mice were not killed by as much as 2 cc. of the neutralized preparation, which could be freed from the effects of the sodium trichloroacetate by dialysis.

However, by precipitation with 68 per cent ethyl alcohol it was possible to obtain a concentration to one twentieth of the original volume. One cubic centimeter of this concentrate from type II meningococcus killed mice. Rabbits given injections of this concentrate over long periods acquired antibodies against the whole organism, as shown by agglutination, precipitin and mouse protection tests. No proteins were present so far as indicated by the biuret test. A positive Molisch test indicated carbohydrate in the extract of every strain examined.

Very noticeable was the irregularity with which this material occurred among the various strains of the organisms and types of organisms. Of the extracts of 12 strains of gonococci examined, only about 6 showed even slight opalescence. A larger percentage of type I and almost all of the type II meningococcus strains gave extracts containing the glycolipoidal compound. No glycolipoidal material was obtained from catarrhalis or from rough or smooth strains of type I pneumococcus. The latter result corresponded to Boivin's findings, as also did our work on S. aertrycke. Our product, like Boivin's, was large in quantity and toxic; 0.2 cc. of the original aertrycke extract was a lethal dose for 20 Gm. white mice.

Tryptic digestion or autolysis before extraction afforded a more abundant trichloroacetic acid extract. Doubling the concentration of acid increased the yield. Regarding time of growth, the yield reached the optimal at the end of fifty hours, remaining the same for many days thereafter.

RELATION OF MANGANESE TO VITAMIN B_1. DAVID PERLA and MARTA SANDBERG, Montefiore Hospital, New York.

Rats given an excess of vitamin B_1 (200 international units daily) may show disturbances in lactation and maternal instinct. This is associated with neglect of the young and cannibalism. The effect is pronounced after one generation. The addition of small amounts of manganese (0.5 to 2 mg.) as manganese chloride completely prevents and cures these symptoms. An excess of vitamin B_1 results in rapid utilization of available manganese, thus creating a relative deficiency of manganese. Metabolic studies are presented that give chemical proof that manganese is essential to the utilization of vitamin B_1. Rats fed a diet rich in manganese but containing inadequate quantities of vitamin B_1 will show signs of acute deficiency of vitamin B_1 more rapidly than rats fed the same diet but low in manganese.

EFFECT OF ELECTROLYTE DISTURBANCE ON RESISTANCE TO HISTAMINE. DAVID PERLA and MARTA SANDBERG, Montefiore Hospital, New York.

An electrolyte disturbance in the blood analogous to that occurring after adrenalectomy was produced in rats by injecting 20 cc. of isotonic dextrose intraperitoneally and withdrawing the fluid after four hours. When tested with histamine, such animals succumbed to the drug in amounts equal to one-half that of the minimum lethal dose for normal rats. The drop in resistance, however, was not as severe as after adrenalectomy.

Normal rats receiving 20 cc. of physiologic solution of sodium chloride four hours before the injection of histamine survived an amount twice the minimum

lethal dose for untreated animals. Feeding salt in the diet during a period of several days before the test definitely increased the resistance of normal rats to histamine. The significance of these findings for the prevention of operative shock and for the treatment of infection is discussed.

AMINO ACIDS IN PLASMA PROTEIN FORMATION. SIDNEY C. MADDEN, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

In the regeneration of blood plasma proteins in the standardized hypoproteinemic dog, gelatin is of little value. When cystine together with either tryptophan or tyrosine is added with the gelatin, the combination becomes as potent in plasma protein regeneration as any protein tested to date. Methionine cannot substitute for cystine in this reaction nor can phenylalanine substitute for tyrosine. In another species (rat) it has been shown by Rose that both methionine and tyrosine are, and cystine and phenylalanine are not, essential for growth.

PASSAGE OF TYPE III PNEUMOCOCCI FROM THE BLOOD STREAM INTO THE JOINTS AND CERTAIN OTHER BODY CAVITIES OF THE RABBIT. GRANVILLE A. BENNETT and MORRIS F. SHAFFER, Harvard Medical School, Boston.

By means of suitable technics, the passage of pneumococci from the blood stream into certain body cavities of the rabbit has been investigated. Within twenty-four hours after intravenous injection of rabbit-virulent strains of Pneumococcus type III, most animals present infections of one or both knees. The frequency of involvement of both knee joints increases with the duration of the disease. The spinal fluid, ocular aqueous fluid and bladder urine remain free of type III pneumococci at a time when the knee joints are already affected. Subsequently, however, they too may be invaded. The administration of type-specific antipneumococcus horse serum at a period when in all probability one or both knee synovia contain organisms appears to be ineffective in bringing about resolution of the infectious process in these sites, even though horse serum constituents may be demonstrated serologically to be present within the joint cavities.

EFFECT OF REPEATED TRANSFUSIONS ON THE SERUM PHOSPHATASE OF DOGS WITH PARTIAL AND COMPLETE BILIARY OBSTRUCTION. STEPHEN MADDOCK, SIEGFRIED THANNHAUSER, MAX REICHEL and NICHOLAS BONCODDO, Surgical Research Laboratory of the Boston City Hospital and the Boston Dispensary, Boston.

In a series of dogs the common bile duct was ligated in order to cause a rise in serum phosphatase as previously described by Bodansky and ourselves. This procedure ordinarily causes a rise from the normal of $\pm$ 1.5 units to $\pm$ 100 units in about fourteen days, but the height of the rise varies greatly with the individual animal. At the end of this period there is a gradual decline in the serum phosphatase. In the present experiments the animals were given transfusions of blood from normal dogs at varying intervals. The amount of blood given corresponded to approximately 20 per cent of the calculated blood volume. No significant changes were noted for twenty to twenty-four hours, but at this time there was definite augmentation of the phosphatase values, which often continued for three to five days. In some instances there was a drop twenty-four hours after the transfusion. These results are in marked contrast with those of Freeman and Chen, who gave blood from jaundiced dogs to normal animals. The theoretic reason for this will be discussed.

By frequent transfusions it was possible to maintain a serum phosphatase value of over 200 Bodansky units for more than two months and to attain values as high as 360 units per hundred cubic centimeters. The exact optimum interval for transfusions has not as yet been determined. In general, dogs which are given

transfusions remain in better clinical condition and live longer after complete biliary stasis than control animals which are not given transfusions. No definite changes in bones have been found in dogs with high serum phosphatase surviving as long as three months.

In some animals plasma or packed (not washed) red cells alone were given. It would seem that plasma has a greater augmenting effect than red cells. When normal and icteric serums or whole bloods were mixed in varying proportions and incubated at 37 C. for twenty-four hours under sterile conditions an increase in phosphatase comparable to the animal experiments was found.

In some animals the hepatic ducts were ligated after the technic of McMasters and Rous (1921) so as to obstruct approximately three fourths of the extrahepatic biliary system. This operation does not produce clinical jaundice but a rise in phosphatase which parallels that of complete obstruction was found. After about fourteen days this increase declined and reached a normal value in about twenty-eight days. This finding is another indication of the difficulty of using phosphatase values in clinical medicine as a means of differential diagnosis in various types of jaundice.

ROLE OF THROMBOPLASTIN IN BLOOD CLOTTING. EDWIN T. MERTZ, W. H. SEEGERS and H. P. SMITH, University of Iowa, Iowa City.

Data are presented to show the amount of thrombin formed on mixing thromboplastin and prothrombin in varying proportions and allowing the reaction to proceed to completion. When either reacting substance is present in excess, the amount of thrombin formed varies markedly with the amount of the other reacting substance added. This fact speaks against an enzymatic interpretation of the reaction. The mechanism of the activation of prothrombin by thromboplastin appears to be chemical in nature.

RATE OF THROMBIN FORMATION IN NORMAL AND IN HEMOPHILIC BLOOD. K. M. BRINKHOUS, E. D. WARNER and H. P. SMITH, University of Iowa, Iowa City.

The rate at which prothrombin is converted into thrombin in whole blood and in serum has been determined. Although the blood clots in a few minutes, a number of hours is required for the complete conversion of prothrombin into thrombin. The amount of thrombin present at any moment represents a balance between thrombin formation and thrombin destruction. At no time during conversion does the thrombin titer exceed 1 or 2 per cent of the total theoretically possible if antithrombin were absent.

Hemophilic blood is compared with normal blood in these respects. The prothrombin conversion rate is slowed in hemophilia, and the thrombin concentration at any one time is much less than in normal blood. This slowed conversion rate of prothrombin can be brought to normal by the addition of extremely small amounts of a thromboplastic organ extract.

INFLUENCE OF LIVING OMENTAL AND MUSCLE GRAFTS ON THE KIDNEY. HARRY A. DAVIS, University of Tennessee, Memphis.

In a series of dogs a study was made to determine the effect of the production of an accessory blood supply to the kidney on its structure and function. Omentum and also muscle (rectus abdominis) with intact vascular supply were implanted into one kidney and fixed with catgut sutures. At intervals varying from ten days to six weeks renal function tests were performed, after catheterization of the ureters from kidneys operated on and those not operated on. Intravenous injections of isotonic dextrose or of sodium chloride solutions produced more rapid and greater

(5 to 100 per cent increase) diuresis from the kidney operated on. Urea clearance and phenolsulfonphthalein tests revealed a greater output from the vascularized kidney. The specific gravity of the urine from the altered kidney tended to be somewhat lower than that from the opposite kidney. The kidney with the accessory circulation diminished somewhat in size, and microscopic examination revealed partial fibrous connective tissue replacement of the graft, relative increase in the number of glomeruli and marked dilatation of the renal tubules. The omental graft appeared to be more efficacious than the muscle graft.

NEW YORK PATHOLOGICAL SOCIETY

ALFRED PLAUT, *President*

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CHARLES T. OLCOTT, *Secretary*

TRUE HERMAPHRODITISM. MILTON HELPERN.

True hermaphroditism was encountered at necropsy on the body of a 37 year old Negro, who died of alcoholism and was brought to the Office of the Chief Medical Examiner. The subject had grown up as a boy and man and had been married twenty years. The libido was masculine, and coitus was performed frequently and satisfactorily, according to the wife, who had never been pregnant. No other history was obtainable.

The body was slender, 5 feet 4 inches (162.5 cm.) long, and weighed about 130 pounds (59 Kg.). The face was beardless and the skin of the body smooth in texture. The breasts were feminine, each 15 cm. in diameter and 5 cm. thick; the pubic hair was feminine in distribution. The external genitalia consisted of a short, well formed hypospadic penis, 3.2 cm. long and 2.5 cm. in diameter, with prepuce and glans, and a scrotum. The right scrotal sac contained a globular mass (ovotestis); the left was empty. A small vertical indentation, 3 mm. deep, was found on the glans. The 1 cm. hypospadic urethral meatus was 8.3 cm. from the end of the penis. The right inguinal ring and canal were patent. The left internal inguinal ring and canal were closed.

The internal reproductive organs in the pelvis consisted of a uterus, left tube and ovary. The body of the uterus measured 7 cm. in width, 5.5 cm. in length and 2.5 cm. in thickness. It contained many subserous, interstitial and submucous myomas. It tapered abruptly into an elongated cylindric cervix, 4 cm. long and 2 cm. in diameter. The wall of the cervix was 7 mm. thick; the small cervical lips projected into the vagina; the external os was 2 cm. in circumference. The body of the uterus was lined by endometrium; the cervical canal and vagina contained blood-tinged mucus. The vagina was a cylindric canal, 6.2 cm. long and 1.3 cm. in diameter; its distal end opened into the urethra through a 2 mm. orifice situated on the left side of the urethral floor 3.8 cm. from the bladder and 5 cm. from the urethral meatus, the latter distance being the length of the urogenital sinus. The proximal portion of the urethra was surrounded by a sphincter of smooth muscle without glandular tissue.

The left fallopian tube was 9 cm. long and 3 to 5 mm. in diameter; its medial end arose from the upper left corner of the uterus. The left round ligament was inserted into the closed left internal inguinal ring. The ovary, located behind the left broad ligament and suspended by a mesovarium and ovarian ligament, measured 2.5 by 2.2 by 1.6 cm.; its surface was nodular and uneven. It contained a large corpus luteum 1.6 by 1.3 by 1 cm. and two smaller corpora lutea. Microscopically there were numerous corpora albicantia and fibrosa, sclerotic blood

vessels and occasional primary graafian follicles. The hilus of the ovary contained a well developed plexus of ducts, the rete ovarii, identical in appearance with, but more compact than, the rete testis found in the ovotestis on the right.

No fallopian tube or separate ovary was found on the right side. A round ligament, 12.5 cm. long and 2 mm. in diameter, extended from the upper right corner of the uterus into the dilated right inguinal ring. Near the inguinal ring it joined a thicker cord containing fat and the testicular artery and veins, which passed through the inguinal canal into the right scrotal sac, where it was attached to the ovotestis. The ovotestis, enclosed in a tunica vaginalis, was small, measuring 2.3 by 1.3 by 1 cm., and had the shape of a testis. The ovarian tissue at one pole was not recognizable grossly. The tunica albuginea was thin and smooth. On section the testicular substance was mottled yellowish brown and separated into lobules by whitish septula. Four pedunculated hydatids (appendices epididymidis), two long and two short, were attached to a mass of fat tissue adjacent to the pole of the testis capped by ovarian tissue. No nonpedunculated hydatid (appendix testis) was found on the testis. Microscopic examination of the ovotestis revealed a layer of ovarian tissue capping one pole, composed of typical stroma containing corpora fibrosa and a small cyst devoid of epithelium, but no ova. The adjacent testicular tissue had the appearance of a cryptorchid. There were numerous seminiferous tubules, each with a thickened and hyalinized basement membrane, lined by layers of cells with clear cytoplasm but without evidence of spermatogenesis. The interstitial tissue was increased and infiltrated with large clumps of interstitial cells. The rete testis was prominent and similar in structure to, but less compact than, the rete ovarii on the left. No definitely recognizable epididymal ducts were found. Vas deferens, prostatic tissue and seminal vesicle were not found. The pelvic brim was almost circular in outline, measuring 12 cm. by 11.5 cm. The larynx was small. None of the other organs revealed any significant changes.

This case may be classified as one of true unilateral hermaphroditism with an ovotestis on the right and an ovary on the left. According to the more cumbersome classification of Klebs, it belongs in the group hermaphroditismus verus completus femininus sinister with conjoined ovotestis on the right and ovary on the left.

DISCUSSION

ALFRED PLAUT: It is too bad that there were no studies of the hormones. Did you try to elicit anything about cyclic behavior?

MILTON HELPERN: As far as I could learn from his wife, who was rather reluctant to talk about him and who seemed to be very naive about the matter, the man seemed masculine in his traits, and as far as his libido and his conduct during coitus were concerned, she said he seemed to be all right! During his alcoholic "sprees" she knew very little about what he did or where he went. The anatomic findings certainly indicate that he menstruated, but I could not obtain any information about this phenomenon from his wife.

ROBERT A. MOORE: May I ask if the cyst at the upper end of the ovotestis was lined with squamous epithelium?

MILTON HELPERN: No, it is not lined by squamous epithelium. I should like you to look at it under the microscope.

ROBERT A. MOORE: I thought perhaps it represented an appendix testis.

MILTON HELPERN: I did not mention that there were four pedunculated appendixes on the mass of tissue which I thought at first was epididymis; a nonpedunculated appendix, a derivative of the müllerian duct, was not found on the testis. Apparently the testicular portion of the ovotestis had completely suppressed the müllerian duct structures on the right side, the pedunculated appendixes of the epididymis being derived from the wolffian duct or body and not from the müllerian duct.

A Case of Rhabdomyosarcoma of the Fundus Uteri. N. Chandler Foot.

The case concerns a patient of Dr. Charles E. Farr, who gave me permission to present it. The patient is a woman of 65. She began to have a mild serosanguinous discharge from the vagina three months prior to admission. This progressed until she was flowing steadily and passing blood and foul material. She lost 20 pounds (9 Kg.) in weight. Her menopause was "many years ago." Her family history and present history are not contributory, and the results of her physical examination were negative except for a uterus with the fundus near the umbilicus. A mass 3 cm. in diameter protruded from the external cervical os. Examination of this in the laboratory showed it to be too necrotic for diagnosis, but some large cells suggested sarcoma. Curettage was advised and carried out, resulting in the removal of 177 Gm. of indescribably foul-smelling slough. Microscopic examination of this revealed a few viable bits of tumor, unmistakably rhabdomyosarcoma.

During eighteen days 1,100 roentgens of radiation were delivered through each of two portals, causing the uterus to subside to almost normal proportions. Panhysterectomy was then carried out.

The specimen measured 9.5 cm. in axial length, including the cervix. It was 7 cm. wide and 3 cm. thick. It was somewhat soft in consistence, and it bulged on the left margin beneath the cornu. On section a large white soft tumor mass was found to spring from the fundus, hanging from its anterior aspect into the endometrial lumen. It was somewhat laminated and measured about 4 cm. in diameter.

Microscopic examination revealed a loose architecture of pleomorphic cells; fusiform, ribbon-like, squash-shaped and giant multinucleated forms were demonstrable. There was little intercellular matrix. In many of the ribbon-like cells and a few of the larger, squash-shaped forms in sections treated with Masson stain and, more particularly, in sections prepared with Mallory phosphotungstic acid stain, cross striations were demonstrable. Mitotic figures were abundantly present and very atypical in many instances. The tumor invaded the myometrium of the fundus to a very slight extent, being superficially situated.

The pathologic aspects of the rhabdomyosarcoma are not obscure if one focuses attention on the prominent coarse nuclei of the cells, with their often enormous nucleoli, and is not too insistent on the demonstration of cross striations. As these do not at once develop in the embryo, it is possible that many very primitive tumors of this category reproduce stages in muscular development that antedate the formation of striations. Striations, however, clinch the diagnosis.

Tumors of this type are not well discussed in the average textbook of gynecology or obstetrics on account of their rarity and the habit of textbook compilers of carrying over old descriptions from one edition to another. They are mentioned under the heading "Botryosarcoma" or "Sarcoma Botryoides," a type of tumor which is more often found in the cervix and vagina of girls and which may be a mixed tumor and somewhat different from the true rhabdomyosarcoma of the fundus uteri of the elderly woman. The latter is thought to arise in a displaced rest from the dorsal myotome.

DISCUSSION

Amour F. Liber: I think the prompt and marked response to radiation of a rhabdomyosarcoma which showed such highly differentiated muscle cells as this, with cross striations, is of great interest, because normal muscle tissue is generally among the tissues most resistant to radiation, and, furthermore, the general statement which is made less often at present than it used to be that radiosensitivity is inversely proportional to differentiation seems to be once more proved untrue in this case.

Milton Rabson: I should like to ask if there were any areas of benign character such as are seen in myoblastoma of the tongue.

N. CHANDLER FOOT: In regard to the differentiation, I think it is a little misleading, because one does not see the cells differentiated to the point of cross striation except here and there. Cross striation is not seen in the majority of instances, so that the differentiation in this case is a sort of freak differentiation, and, as one could see from the shape of the cell I showed, it is a far cry from such a cell to the normal muscle fiber. I agree as to the radioresistance of well differentiated muscle tissue, but I think this tissue can scarcely be called well differentiated. Occasional cells go the limit as far as cross striations are concerned, but, even so, their morphologic character is far from normal.

As to the question of a benign form, such as that seen in myoblastoma of the tongue, there was no vestige of anything of that sort in this tumor. It was made up of edematous, lawless tissue which broke down easily and which was typical of myosarcoma once it broke into a cavity. I have noticed that a rhabdomyosarcoma on the leg grew rapidly in situ, to be sure, but once a biopsy was made through the fascia and the tissue escaped through the incision, almost a handful of tumor tissue would grow into the dressings every day. Such tumors have a habit of growing luxuriantly and breaking down as fast as they grow.

AMOUR F. LIBER: Were there any undifferentiated mesenchymal cells? Could the tumor be interpreted as a composite growth which was differentiating into muscle cells?

N. CHANDLER FOOT: I can give the legal answer, "yes and no." There were small undifferentiated cells among the muscle cells. I think they were a very young form of myoblast.

PERINEURIAL FIBROBLASTOMA RATHER THAN SCHWANNOMA: "DIRECT STAINING" EVIDENCE AGAINST THE SCHWANN CELL ORIGIN. I. M. TARLOV (by invitation).

The hypothesis of the schwannian origin of the common encapsulated tumor of nerves was put to test by a direct staining method for Schwann cells—Dockrill's modification of Rio Hortega's silver impregnation technic (Penfield, W.: *Am. J. Path.* **6**:445, 1930). By means of this technic Schwann cells which occur along the nerve fibers in neurofibroma of the von Recklinghausen type were clearly impregnated, whereas the type cell of this tumor, which is the same as the type cell of the solitary tumor (perineurial fibroblastoma, schwannoma or neurilemmoma), proved to be of a totally different type—elongated, like a fibroblast. The contrast between the Schwann cell of the nerve fiber and the type cell of the tumor was clearly shown in a single microscopic field. The technic was applied directly to the solitary encapsulated tumors, whose cells proved to be elongated like fibroblasts and totally unlike Schwann cells. By means of this technic, proliferating Schwann cells which occurred in a traumatic neuroma of the ulnar nerve were clearly impregnated. The inability to impregnate Schwann cells in the solitary encapsulated tumors of nerves by this technic, which brings out normal and proliferating Schwann cells, is interpreted as disproving the schwannian origin of these tumors. The fibroblastic origin of these tumors is accepted in view of the morphologic resemblance of their cells to fibroblasts and the rich reticulin stroma, which suggests the endoneurium. Attempts to show that reticulin formation may be provoked by Schwann cells are not considered conclusive. For example, Masson, as evidence to support the view that Schwann cells may provoke the formation of reticulin without the intervention of fibroblasts, cited Nageotte's demonstration that reticulin occurs along the central prolongations of nerve fibers through the pial ring in the same distribution as the membrane of Schwann. Nageotte was of the opinion that fibroblasts did not occur in this region and hence that they were not necessary for the formation of reticulin. However, I (Tarlov, I. M.: *Arch. Neurol. & Psychiat.* **37**:555, 1937) pointed out that this argument is not valid, since I was able to demonstrate fibroblasts central

to the pial ring along the same distribution as reticulin. The fibroblast is the one cell which is constantly found in association with reticulin of the endoneurium.

Although endoneurium may give rise to these tumors (as indicated by their occurrence in 2 cases along portions of the vagus nerve roots, which are devoid of perineurium), it seems wise to retain Mallory's term, "perineurial fibroblastoma," for these tumors. The occurrence of nerve fibers within an encapsulated tumor of peripheral nerves, although usually considered characteristic of multiple neurofibromatosis, was encountered within one of the solitary perineurial fibroblastomas of the vagus nerve which was reported.

DISCUSSION

N. CHANDLER FOOT: Dr. Tarlov has pleaded his case with great eloquence, and I am not going to enter into a detailed argument with him, because I know it would run into time if I did. The chief obstacle in my mind is this: Where in the body are fibroblasts ever found acting like the cells of Verocay bodies except in connection with the nerves? One knows that similar bodies are formed in certain types of schwannoma, particularly in the scalp, the so-called *lames foliacées* of Masson. One knows that these Verocay bodies occur in neurilemmoma (which after all is a rather good term, because it does leave a loophole), and again one knows that whorls not unlike these are formed in meningioma. It seems to me these three types of tumors are linked together morphologically. I think the big stumbling-block is that there is a great deal of connective tissue in connection with the neurilemmoma which is hard to explain. How does it get there? There is yet another stumbling-block: There is still a rather acrimonious dispute as to whether the meninges are ectodermal or mesodermal in origin. The pia and the arachnoid, according to various French authorities, especially Oberling and Masson, are of ectodermal origin, and therefore different from the dura, which is admittedly of mesodermal origin. There have been some very ingenious experiments which seem to prove that. I shall not go into them now because I cannot remember the exact data offhand, but I think the matter will have to be left open until it has been studied more extensively. The first objection in my mind is this: If these cells are fibroblasts, they do not act like fibroblasts, and until I can prove why they should act so differently, I prefer to consider them as specialized cells. As to their being Schwann cells, I think Dr. Tarlov has made a strong point there. Possibly they are not, but if they are not Schwann cells, one has to postulate a new cell intermediate between the Schwann cell and the fibroblast of the perineurium.

AMOUR LIBER: The use of this new staining technic seems to be crucial in this matter, because the other criteria for differentiating the Schwann cells in tumors from fibroblasts which Dr. Tarlov mentioned are really not reliable, particularly the presence of the endoneurial network of reticulin. Dr. Tarlov did mention differences in its interpretation. Nageotte made a number of rather telling arguments, in my opinion, for the nonspecificity of the presence of reticulin or collagen for the discrimination of fibroblasts. One which is perhaps more significant than any other, which was not mentioned, is that the first formation of collagen or reticulin anywhere in the body is in the sheath of the notochord, in other words, in contact with cells of epithelial origin and at a stage in embryogenesis when no fibroblasts are present at that point, or, rather, no mesenchymal cells, so that apparently reticulin is formed in previously undifferentiated interstitial substance in the embryo, under the influence of ferments secreted by various cells. The most common cells that secrete these ferments are the fibroblasts, but there may be many different kinds of cells, the cells of the notochord, perhaps, and cells arising from the neural crest, such as the Schwann cells. Whether the reticulin is really formed from the cells on the outside, the fibroblasts, or whether it is the ferments from one cell or the other which produce this coagulation in interstitial substance, I think, is at present impossible to determine, so that all these criteria apparently fail. If this staining method is specific for oligodendrog-

lia, that should give one hope for the solution. I should like to ask whether Dockrill's method, with which I am not familiar, stains the oligodendroglia of the central nervous system as well.

In connection with von Recklinghausen's disease as a genetic entity, one often finds associated with multiple or solitary perineurial fibroblastoma tumors in the central nervous system and sometimes tumors in the optic nerve. As Dr. Tarlov has pointed out, the latter are not fibroblastoma. They are usually glioma, astrocytoma or spongioblastoma. Tumors which occur in the central nervous system have received curious names, such as "central neurinoma," given by German authors, and often they have the general appearance and the arrangement of cells which one sees in the peripheral nerve tumors except that there is no reticulin or collagen in them. I do not know just what that combination signifies. It may signify merely that one is dealing with a complex expression of a genetic factor resulting in anomalies both of the glia and of the fibroblasts, such as one sees in tuberous sclerosis.

ARTHUR PURDY STOUT: I have approached the problem from a somewhat different angle—that of tissue culture. Three years ago Dr. Margaret Murray, who is here tonight, with whose permission I mention this, determined to try to find out the tissue-cultural characteristics of the Schwann cells, the fibroblasts' characteristics being known. We tried to grow some of these tumors, as well as tumors of von Recklinghausen's disease, in tissue culture. She succeeded after a good deal of effort in learning the cultural characteristics of the Schwann cells so that they could be recognized every time. She then made cultures of about six of these solitary tumors, as well as of the tumors of von Recklinghausen's disease, and in every case the only cells that grew out were the Schwann cells. The only thing we have not yet seen them do is to form reticulin or collagen. This is probably because she could not keep them going long enough without changing the medium. I was not certain three years ago as to whether these tumors were of fibroblastic or schwannian origin. Her work has persuaded me that they are schwannian growths.

I. M. TARLOV: I can understand how one might have doubts in accepting the fibroblastic origin of this tumor. There have been volumes written on it, and most of the evidence presented has been indirect and conflicting. It is true that these fibroblasts behave somewhat differently from other fibroblasts—for instance, those one sees in meningioma—but, after all, they are in a different environment, and may one not expect them to behave differently? Whether one considers the meninges ectodermal or mesodermal does not matter a great deal for the present discussion. One might consider them mesenchymal, that is, chiefly mesodermal with a few ectodermal elements, but these cells do not behave like ectodermal cells. There is a good deal of evidence, for example, that the Schwann cells, which are ectodermal, are homologous with the oligodendroglia, and that this technic brings out both oligodendroglia and Schwann cells is a point much in favor of that. Oligodendroglioma is not associated with reticulin of the type encountered in the tumors under consideration, and on the basis of homology one would not expect real schwannoma to be associated with such reticulin. This is again a bit of indirect evidence against the schwannian origin of such tumors. I am aware that there has been a good deal of experimentation and attempts to prove reticulin is not necessarily related to fibroblasts. I do not know whether one can accept all of it. The evidence with regard to the endoneurium I do not believe stands up. I have seen sections by which in cases of experimental Schwannoma attempts have been made to prove that the endoneurium comes before any invasion of fibroblasts. I have had an opportunity to examine the sections in detail, and I could not feel quite certain that was so. I have tried here merely to present as direct an approach as possible, and it seems to me that the staining is fairly clear. I am much interested in Dr. Stout's evidence, and I do not know what to say in answer to that except that it would be interesting to subject these preparations to the staining technic used in this study.

ABSORPTION AND UTILIZATION OF VITAMIN K: STUDIES IN EXPERIMENTAL ANIMALS AND IN MAN. ROBERT A. MOORE and (by invitation) WILLIAM DEW. ANDRUS, JERE LORD and ISABEL BITTINGER.

The accessory food factor necessary for proper maintenance of the plasma prothrombin, designated as vitamin K, can be easily demonstrated. It is present in relatively large amounts in alfalfa and fish meal, and preparations of it can be purified so that an amount less than a milligram is effective in deficient chicks. The chemical nature of the vitamin as obtained from plant and from animal sources is probably different. The vitamin is present in the feces of animals fed a deficient diet. This would indicate that bacteria in the intestine synthesize an active substance from a provitamin.

In animals and in man bile or bile salts are necessary for proper absorption of vitamin K. In dogs obstructive jaundice or biliary fistula results in a gradual fall in the plasma prothrombin, which may be corrected by oral administration of vitamin K and bile salts.

In addition to the points of proper intake and absorption, a normally functioning liver is necessary for the maintenance of the plasma prothrombin. Thus, in severe hepatic damage caused by infection, obstruction or cirrhosis, vitamin K has little effect.

All patients with jaundice should be carefully studied before operation, and if the plasma prothrombin is low, vitamin K and bile salts should be given.

Book Reviews

Le sérum normal. Propriétés physiologiques. D. Brocq-Rousseu and G. Roussel. Volume 2. Paper. Pp. 630. Price 140 francs. Paris: Masson & Cie, 1939.

This is the second volume on the normal properties of serum. The first volume, dealing with the physical characteristics of normal serum, was published in 1933. The book fulfils a need felt for a long time by physiologists. The authors gathered data dispersed in 3,925 publications in several languages and analyzed them from a variety of angles in 19 chapters, covering 446 pages. The first chapter deals with the antigenic properties of normal serums and with the effect of physical and chemical influences on these properties. There is a brief discussion of the Forssman antigens. In the second chapter the natural antibodies are discussed, e. g., normal tetanus and diphtheria antitoxins, antibodies against staphylococci, pneumococci and the agents causing anthrax, dysentery and poliomyelitis. The question whether antibodies pass through the placenta from the mother to the fetus is considered. A brief chapter is devoted to the ability of normal serum to neutralize bacteriophage. The largest chapter (67 pages of text and 24 pages of bibliography with 546 references) deals with the toxicity of serum. The primary toxicity of the serum of man and of various animals is reviewed with special attention to the serum of the horse, the beef, the sheep, the goat and the dog. The authors summarize the data dealing with: (*a*) the physiologic variations due to state of nutrition, age and special conditions, e. g., pregnancy; (*b*) experimental variations, e. g., the effect of physical and chemical measures, and (*c*) variations in different diseases. The same pattern is followed in the consideration of other properties of normal serum in the remaining chapters. The discussion of secondary toxicity includes hypersensitiveness and anaphylaxis. A chapter on the isohemoagglutinins and heterohemoagglutinins and the bacterial agglutinins is followed by a brief chapter on conglutination and its relation to agglutination. Then come sections on precipitins, cytolysins and opsonins. Thirty-seven pages are devoted to the bactericidal properties of the serum of man and animals, with reference to a variety of pathogenic bacteria, viruses and protozoa. The isohemolysins and heterohemolysins and the leukocytolysins are discussed. Then comes a chapter on complement, its nature and its physiologic, experimental and pathologic variations. The influence of injections of serum on the coagulation of blood, its action on the coagulation of plasma in vitro, the constricting action of serum on the blood vessels and on the smooth muscles of the intestines and of the uterus, the stimulating action of serum on the hemopoietic function of the bone marrow, its nourishing properties as a culture medium and its therapeutic properties are summarized. The last chapter has to do with special qualities of serum that were not considered previously: its influence on autolytic changes in tissues; its relation to the growth and the aging of cells, to cellular metabolism, to the movements of lymphocytes and to sexual characteristics; its action on the toxicity of tissue extracts and of venoms, on antiseptics, on various chemicals and so forth.

The review can give only a slight idea of the wealth of material contained in the book. One could find faults with the book. While the bibliography is large, it is not difficult to detect in it defects, some of them rather glaring. The book lacks an index; a very detailed list of chapters and subchapters helps to overcome the lack of an index but to only a limited extent. One might object also to the occasional repetitions. These slight imperfections do not detract from the real value of the work, which ought to be useful to physiologists and immunologists. The authors promise a third volume on the enzymes of the blood serum.

Books Received

BRUCELLOSIS IN MAN AND ANIMALS. I. Forest Huddleson, D.V.M., M.S., Ph.D., Research Professor in Bacteriology, Michigan State College. Contributor Authors: A. V. Hardy, M.S., M.D., Dr. P.H., Associate Professor of Epidemiology, DeLamar Institute of Public Health, Columbia University Medical School, and Consultant, United States Public Health Service; J. E. Devono, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics, Royal University of Malta; Ward Giltner, D.V.M., M.S., Dr. P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Cloth. Pp. 339, with 40 figures. Price $3.50. New York: The Commonwealth Fund, 1939.

ARCHITECTURE OF THE KIDNEY IN CHRONIC BRIGHT'S DISEASE. Jean Oliver, M.D., Professor of Pathology, Long Island College of Medicine, Brooklyn. Cloth. Pp. 257, with 112 illustrations. Price $10. New York & London: Paul B. Hoeber, Inc., 1939.

BLOOD GROUPS AND BLOOD TRANSFUSION. Alexander S. Wiener, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City. Second edition. Cloth. Pp. 306, with 52 illustrations. Price $5. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, Publisher, 1939.

THE NEUROGENIC BLADDER. Frederick C. McLellan, M.S., M.D., Instructor in Surgery, University of Michigan Medical School, Ann Arbor. Cloth. Pp. 206. Price $4. Springfield, Ill., and Baltimore, Md.: C. C. Thomas, Publisher, 1939.

STUDIES IN EARLY GRADUATE EDUCATION: THE JOHNS HOPKINS UNIVERSITY, CLARK UNIVERSITY, THE UNIVERSITY OF CHICAGO. W. Carson Ryan, Staff Associate, Carnegie Foundation for the Advancement of Teaching. Bulletin 30. Paper. Pp. 167. New York: The Carnegie Foundation for the Advancement of Teaching, 1939.

PUBLICATIONES DEL CENTRO DE INVESTIGACIONES TISIOLOGICAS. Director: Prof. Roque A. Izzo. Vol. III. Paper. Pp. 337, illustrated. Buenos Aires: Pabellon "Las Provincias" Hospital Tornú, 1939.